AMENDED FINAL STATEMENT OF REASONS

Division 4.5, Title 22, Cal. Code of Regulations, Chapter 54
Green Chemistry Hazard Traits

UPDATE OF INITIAL STATEMENT OF REASONS

OEHHA published the Initial Statement of Reasons in December 2010, and held a public hearing on January 30, 2011. The initial comment period ended on February 15, 2011 and OEHHA received 26 comments. An external peer review was also completed in compliance with the California Health & Safety Code section 57004. After consideration of the comments and reviews, OEHHA made the following modifications to the proposed text:

- Slightly amended definitions of “environmental endpoints” and “hazard traits” for clarity. In the definition of “environmental endpoints” the words “for a specific hazard trait” were added after “environmental endpoints” and the words “that indicates the presence of the hazard trait” were added at the end of the definition. The statement “that may contribute to adverse effects in exposed humans, domestic animals, wildlife, or in ecological communities, populations or ecosystems” were added to the definition of “hazard traits”.

- Added the words “contributing to” to the definitions of the hazard traits eutrophication (subsection 69404.2(a)) and loss of genetic diversity (subsection 69404.4(a)) because chemicals contribute to, but are not solely responsible for, the adverse effects covered in the definitions of these hazard traits.

- Added “Neurodevelopmental Toxicity” as a separate hazard trait from neurotoxicity. There are separate and distinct toxicity tests specifically for neurodevelopmental toxicity. This hazard trait specifically impacts infants and children who are sensitive subpopulations that the Department of Toxic Substances Control must consider under Health and Safety Code section 25252, when using hazard-trait information to identify chemicals of concern in consumer products.

- Added Article 7, “Additional Relevant Data”, to capture information that may be included in the Clearinghouse that is useful for chemical evaluations that are conducted under Health and Safety code section 25252. For example, physicochemical properties are typically used in evaluating the movement of chemicals through the environment and into wildlife and humans. Exposure-response information could include cancer

potency factors, Reference Doses, Reference Exposure Levels, or No-Observed-Adverse-Effect Levels. This type of information is used to evaluate the risks posed by chemical hazards.

- Made minor modifications to the sections on “other relevant data” for each of the toxicological hazard traits to be consistent with one another in terms of structural and mechanistic information.

- Amended subsection 69405.2 for “Bioaccumulation” hazard trait to add additional types of evidence, including “the identification of a substance to be bioaccumulative by an authoritative organization; studies which show bioaccumulation in domesticated animal, wildlife or plant tissue; transfer of the chemical up a food web; a trophic magnification factor or biomagnifications factor greater than 1 in aquatic or terrestrial systems, …or a log octanol-air coefficient greater than or equal to 5; results from bioaccumulation models indicating potential for bioaccumulation; structural similarity to other bioaccumulative chemicals.”

- Added language to subsection 69406.3(b) on the “Flammability” hazard trait to include additional U.S. based criteria.

- Made various minor, non-substantive wording and punctuation changes throughout to ensure clarity and consistency.

OEHHA published the modified proposed regulation on July 29, 2011, together with a notice for a second comment period which ended September 12, 2011. Fifteen comments were received. After reviewing the new comments, OEHHA further modified and augmented the proposed regulation. The changes were as follows:

- Amended the title of Chapter 54 by inserting after “Green Chemistry Hazard Traits” the words “for California’s Toxics Information Clearinghouse”.

- Inserted the word “other” in front of “Toxicological Hazard Traits” in the title of Section 69403.17 to be consistent with that section.

- Reworded a sentence under Section 69401.1 to clarify the intent of the regulation. In the statement that the “chapter provides a structure for relating scientific information to the hazard traits, and for deciding general guidance on whether or not a given chemical exhibits a hazard trait based on the scientific evidence”, the words “for deciding” were replaced with “general guidance on”. In the sentence “(T)hese data can be observed through scientific study and provide less-direct but useful evidence of the presence of a hazard trait”, the word “potential” was added before the word “presence”.

- Corrected a typographical error in subsection 69405.2(b) “evidence for the bioaccumulation hazard trait” by inserting the corrected value for the log

octanol water partition coefficient. In the previous version the number 5 was struck out and the number 4 should have been inserted in its place but was not.

- Added text to Section 69405.3 explaining that evidence for environmental persistence includes "the identification of a substance to be persistent by an authoritative body." Many authoritative organizations have reviewed the scientific evidence and identified substances that are persistent.
- Fixed various punctuation and grammatical errors.

Additional material supporting the amended proposed regulation was also included in the modifications.

OEHHA published a notice for a third comment period which ended October 24, 2011 Six comments were received. No modifications were made on the proposed regulation based on these comments. Responses to these comments are included in the Final Statement of Reasons.

For purposes of completeness, OEHHA added a reference to its existing general authority to adopt regulations.

SUMMARY AND RESPONSE TO COMMENTS RECEIVED DURING THE INITIAL COMMENT PERIOD OF DECEMBER 17, 2010 THROUGH FEBRUARY 15, 2011.

Comments were received from the following organizations:

American Chemistry Council (ACC)
American Cleaning Institute (ACI)
Amway
California Department of Public Health (CDPH)
Californians for a Healthy and Green Economy (CHANGE)
California Nano Industry Network (CalNIN), submitted by Thomas Jacob, TR Jacob Associates
Clean Water Action (CWA)
Dow Chemical Company (Dow)
E.I. DuPont de Nemours and Company (DuPont)
Assembly Member Mike Feuer
Grocery Manufacturers Association (GMA)
Green Chemistry Alliance (GCA)
Koch Industries, Inc. (Koch)
Dr. Amy D. Kyle, School of Public Health, University of California (UC), Berkeley
MBA Polymers, Inc.

Nanotechnology Coalition (Coalition), a trade associated affiliated with the Society of Chemical Manufacturers and Affiliates (SOCMA)
North American Insulation Manufacturers Association (NAIMA)
North American Metals Council (NAMC)
Natural Products Association
Natural Resources Defense Council (NRDC) and the Environmental Working Group (EWG)
Personal Care Products Council (PCPC)
Physicians Committee for Responsible Medicine (PCRM)
Proctor and Gamble (P&G)
Rubber Manufacturers Association (RMA)
Dr. Megan Schwarzman, Berkeley Center for Green Chemistry, UC Berkeley
Sierra Club California

ACC, ACI, Dow, DuPont, GMA, Koch, PCPC, P&G, and RMA were also signatories on the GCA comments.

Comments on the proposed regulation received during the public comment period (December 17, 2010 – February 15, 2011) are provided below, followed by OEHHA's responses. Some comments received were not relevant to this rulemaking. For example, some comments addressed broader issues concerning California's Green Chemistry program, or were specific to the Department of Toxic Substances Control's on-going rulemaking process. These are identified and briefly responded to below.

General Comments

1. Comments on need for coordination with DTSC regulations on Green Chemistry

Several comments expressed concern about an apparent lack of coordination between OEHHA's specification of hazard traits to be included in the Toxics Information Clearinghouse and the Department of Toxic Substances Control's (DTSC) development of its proposed regulations for implementing AB 1879. For example, GCA writes:

> "The Green Chemistry Alliance (GCA) questions OEHHA proceeding with regulatory action related to Green Chemistry Hazard Traits in light of Secretary Adams' announcement of December 23, 2010 directing the Department of Toxic Substances Control (DTSC) to take additional time to develop regulations for the California Green Chemistry Initiative."

Similar concerns regarding coordination with DTSC's regulation for implementing AB 1879 were expressed by the ACC, Amway, GMA, Koch, P&G and Dow.

GCA commented that it is important for the Brown Administration to have input regarding the path forward for the overall Green Chemistry Initiative. The comment states that the:

> "…OEHHA regulation will define content for the Toxics Information Clearinghouse (TIC) and identify considerations for "Chemicals of Concern" listings. Without clarity on the regulatory structure into which the traits must fit, there is too much uncertainty regarding both their operative impact and sufficiency. …GCA is concerned that the gray areas between the responsibilities of CalEPA, DTSC, and OEHHA are critical issues that must be discussed and resolved prior to finalizing this proposed regulation."

Other comments (ACI, PCPC, CalNIN) indicated that the DTSC regulation and the approach they are going to take to implement AB 1879 should inform the OEHHA regulation regarding SB 509 Clearinghouse traits. One noted that AB 1879 and SB 509 require DTSC to develop criteria by which chemicals and alternatives are evaluated that include the hazard traits, endpoints and other relevant data in the Clearinghouse. They asked that OEHHA stop moving forward on the SB 509 regulation until DTSC decides how they will use the clearinghouse information to evaluate chemicals.

Response: OEHHA has consulted with DTSC in developing the hazard traits regulation as required by SB 509. DTSC reviewed the regulation and concurs with its format and content.

SB 509 requires OEHHA to evaluate and specify the hazard traits, toxicological and environmental endpoints and other relevant data to be included in the Toxics Information Clearinghouse. Under AB 1879, DTSC considers, among other things, these hazard traits, endpoints and other data in the Clearinghouse when they identify and prioritize chemicals of concern. Completion of the hazard trait regulation prior to DTSC's adoption of its regulation may in fact inform DTSC's development of a regulatory process for prioritizing chemicals and conducting alternatives assessments. No changes were made to the regulation based on these comments.

2. Comments supportive of regulation:

Some comments supported the regulation.

CDPH writes:

"OEHHA has laid out a useful framework for organizing relevant information on the hazards of toxic chemicals. The proposed categories cover all the health effects commonly seen in environmental and occupational public health and medical practice. This approach will be valuable to a wide range of users."

Dr. Kyle writes:

> "The proposal provides authoritative references to support the traits included. It also provides definitions keyed to those used in authoritative sources. This places this review within the evolution of knowledge and practice in this area. It advances the state of the art in this area by considering and building upon definitions put forward over time by other authoritative entities. The traits reflect gains in scientific knowledge in recent years… The proposal represents a more scientifically valid starting point than older references such as the "CMR" list that dates from the 1960s.
>
> "The proposal discusses the types of information that might be considered relevant for each hazard trait. This is very important in contributing toward a transition toward use of more modern methods for assessing chemicals. The National Academy of Sciences has recommended that a transition be made to incorporate newer methods and more current scientific understanding. …The proposal contributes toward this by discussing kinds of information that might be considered for the different traits."

Dr. Schwarzman writes:

> "OEHHA's current proposal provides an essential first step toward establishing the TIC and identifying chemicals of concern to the state of California. This forward-looking proposal defines hazard traits, and is independent of any recommendations for chemical screening… OEHHA has created a robust framework for understanding how chemicals can pose hazards to human health and the environment by building on those traits identified by authoritative bodies in the California, the U.S., Canada and Europe. OEHHA has brought contemporary scientific evidence to bear on these lists by including traits such as epigenetic effects, key ecotoxicological hazard traits, and endpoints that can serve as upstream indicators of hazard."

Sierra Club California writes:

> "This regulation, which is mandated by SB 509, is integral to the process of making consumer products safer in California because it will define what types of human health and environmental hazards may be used as a basis for selecting a product for inclusion in the Safer Alternatives process, and will also specify the data to be included in the state's Toxics Information Clearinghouse."

Response: The comments are noted. The regulation specifying the hazard traits, endpoints and other relevant data has been developed to accommodate all types of information, not just information generated by older toxicity testing paradigms.

No changes to the regulation were made based on these comments.

3. Comments on using existing systems as the Hazard Traits for the Toxics Information Clearinghouse

Several comments were received supporting the broad framework of hazard traits in the regulation, while several other comments recommended adopting or adapting various existing classification systems and data reporting templates.
For example, GCA writes:

> "Several existing hazard trait and toxicological end-point regimes currently in existence nationally and internationally are widely in use and could be easily leveraged by California in harmony with existing practice. The hazard criteria proposed by the US Occupational Safety and Health Administration (OSHA) to modify its existing Hazard Communication Standard (HCS) to conform with the United Nations' (UN) Globally Harmonized System of Classification and Labeling of Chemicals (GHS; *74 FR 50279*, September 30, 2009) constitute one set of hazard traits that will be widely used in commerce in the US and across the globe."

GCA also suggests using the OECD (Organization for Economic Co-operation and Development) Harmonized Templates for Reporting Chemical Test Summaries as standard data formats which are used for reporting chemical test data to the USEPA (US Environmental Protection Agency) and for data requirement in the European Union and OECD High Production Volume Chemical Challenge Programs, and the European Union's REACH (Registration, Evaluation, Authorization and Restriction of Chemical Substances) chemical management program.

> "GCA is concerned that having a new California-only system as proposed under the draft regulation is inefficient, duplicative, and will make it unnecessarily

> difficult to leverage existing information on chemicals. Leveraging these existing systems will provide a framework for things like the use of categories, tiered testing, acute vs. chronic toxicity, judging study quality/reliability, and weight of evidence approaches, all of which are inadequately addressed at all in OEHHA's proposed regulation."

Similar comments that the regulation should leverage or use existing systems from other organizations were provided by the signatories of the GCA comments that individually submitted comments: Amway, DuPont, GMA, Koch, Natural Products Association, PCPC, P&G, and Dow.

Koch, while indicating it supported the GCA comments, also stated:

> "California should align with existing systems, such as Health and Environmental Research Online (HERO) or Organisation for Economic Co-operation and Development (OECD), rather than creating a California stand-alone system (an independent state-based classification system that will not enhance existing data available and result in a waste of resources)…OEHHA has not provided sufficient justification as to why existing systems might be inadequate."

Other comments supported OEHHA's approach to specifying hazard traits, toxicological and environmental endpoints, and other relevant data:

> "The marketplace will function much more efficiently if everyone has access to as much information about chemical hazards as possible. For this reason, we support a very broad "casting of the net" for data points to include in the TIC…there is no reason to limit any relevant hazard data that already exists in the peer-reviewed literature. The work of authoritative bodies should be included so California takes advantage of useful work done elsewhere." (CHANGE)

> "By proposing to go further than REACH or UN's Globally Harmonized System, the TIC will enable more preventive solutions to the health and environmental challenges posed by our society's widespread use of chemicals. " (CHANGE)

> "By including a broad array of hazard traits that impact both human and environmental health, this proposal fills in an extensive data gap that has been neglected by other authoritative bodies and forums. " (CWA)

> "While California's Proposition 65 has been an important guideline to help identify toxic chemicals, the reality is that the health effects of toxic chemicals go beyond cancer and reproductive harm… Our current limited understanding of the health

> and environmental effects of chemicals in products and processes hampers our ability as a society to address problems by avoiding toxins and designing safer chemicals and products. " (CWA)
>
> "The OEHHA proposal also discusses the use of findings by authoritative bodies…This contributes to the Legislature's goal to rely on existing information and determinations as much as possible. (Dr. Kyle)

Response: Before discussing the alternatives proposed in the comments, some clarification of the mandate provided to OEHHA in Health and Safety (H&S) code §25256.1 (SB 509) is necessary.

Understanding the division of responsibility between OEHHA and DTSC in SB 509 (and its companion measure, AB 1879) requires a careful reading of the statutes. SB 509 requires that OEHHA specify the hazard traits, toxicological and environmental endpoint and any other relevant data to be included in the Toxics Information Clearinghouse Relative to DTSC, the statute says: "The department [DTSC] shall establish the Toxics Information Clearinghouse", which "shall provide a decentralized, Web-based system for the collection, maintenance, and distribution of specific chemical hazard trait and environmental and toxicological end-point data." (H&S code §25256)

Other important aspects of SB 509 and AB 1879 are DTSC's responsibility. For example, AB 1879 provides that:

> "[DTSC] shall develop criteria by which chemicals and their alternatives may be evaluated. These criteria shall include, but not be limited to, the traits, characteristics and endpoints that are included in the clearinghouse data pursuant to Section 25256.1." (H&S code §25252(b)(1))

GCA's comment regarding leveraging existing systems to provide a framework for things like the use of categories and judging study quality/reliability, largely pertains to DTSC's mandated responsibility for developing chemical-evaluation criteria, as opposed to OEHHA's responsibility to specify hazard traits, endpoints and other relevant data for the Toxics Information Clearinghouse. Nothing in the OEHHA regulation prevents DTSC from using existing chemical-classification systems to develop criteria for evaluating chemicals under its Safer Consumer Products Regulation.

SB 509 requires OEHHA to develop a product that is unique. The term "hazard trait" is not used in any classification system or database in the world, to OEHHA's knowledge. No systems exist that define hazard traits, per se, or that cover the full spectrum of hazards and endpoints that are important considerations for the DTSC consumer-products regulatory program. There are no other frameworks available that lay out, in a

structured way, hazard traits, toxicological and environmental endpoints and other relevant data that would meet the needs of DTSC's program. OEHHA considered various textbooks, chemical test data entry templates, hazard classification systems, guidelines, and other products while developing the regulation. This has been discussed in the Initial Statement of Reasons and is briefly discussed below. But none of these sources by itself fully meets the requirements of the SB 509 mandate to identify hazard traits, endpoints and other relevant data for use in the Toxics Information Clearinghouse and consumer-products program mandated in SB 509 and AB 1879.

Specific suggestions in the comments are discussed below.

i. Take as hazard traits the hazard criteria proposed by OSHA to modify its existing Hazard Communication Standard (HCS) to conform with the Globally Harmonized System of Classification and Labeling of Chemicals (GHS).

Response: GHS is primarily a general classification system that provides criteria for determining hazards associated with chemicals in commerce. GHS emphasizes physical hazards that are important to the transportation of chemicals and worker health and safety. In 2009, OSHA proposed a rule to change its Hazard Communication Standard based on GHS, but has not finalized the rule. GCA suggests the OEHHA regulation use the hazard traits named in the proposed OSHA adaptation of the GHS. In the proposed rule, there are 10 human health hazard categories.

Using the OSHA adaptation as a source of hazard traits has similar limitations as the GHS, as explained in the Initial Statement of Reasons. The Hazard Communications Standard requires that chemical manufacturers and importers evaluate the chemicals they produce or import and provide hazard information to downstream employers and workers by putting labels on containers and preparing safety data sheets, and the OSHA adaptation of GHS is similarly directed to this end of providing chemical-hazard information to workers. It is <u>not</u> oriented toward the full suite of toxicological and environmental hazard traits and endpoints of concern to the users of consumer products, nor does it address hazards to the general population and environment that result throughout the lifecycle of a product's production, use, disposal, and environmental breakdown.

Most critically, OSHA's proposed rule specifically excludes consumer products or hazardous substances,[1] which makes the rule an inappropriate choice as the

[1] **(b)(6)(ix)** Any consumer product or hazardous substance, as those terms are defined in the Consumer Product Safety Act (15 U.S.C. 2051 et seq.) and Federal Hazardous Substances Act (15 U.S.C. 1261 et seq.) respectively,

basis for specifying hazard traits for chemicals in consumer products.

As shown in the table below, none of the hazard criteria in OSHA's 2009 proposed rule address environmental or exposure potential hazard traits. These will be important considerations for the DTSC regulatory program, which may need to consider whether a chemical of concern will bioaccumulate, affect wildlife survival, deplete the ozone layer, and so forth. Further, the list of human health hazards in the proposed OSHA rule provides detailed hazard information on endpoints of greatest concern for workers that receive exposures to chemicals at typically much greater levels than would be acceptable in consumer products.

The OSHA adaptation of GHS lumps all organ-specific toxicity as "specific target organ toxicity single exposure" or "specific target organ toxicity repeated or prolonged exposure" and sets out a system for classification and labeling for certain applications. While information in the OSHA setting may be useful for occupational health and safety, systemic toxicity is an overarching and vague description of the capability of a chemical to induce adverse responses in an organism and does not provide any detail on which organs are affected,

Hazard Criteria in OSHA 2009 Proposed Rule Based on GHS	
Health Hazard Criteria	Physical Hazard Criteria
1 acute toxicity 2 skin corrosion/irritation 3 serious eye damage/eye irritation 4 respiratory or skin sensitization 5 germ cell mutation 6 carcinogenicity 7 reproductive toxicity 8 specific target organ toxicity single exposure 9 specific target organ toxicity repeated or prolonged exposure 10 aspiration hazard	1 explosives 2 flammable gases 3 flammable aerosols 4 oxidizing gases 5 gases under pressure 6 flammable liquids 7 flammable solids 8 self-reactive chemicals 9 pyrophoric liquids 10 pyrophoric solids 11 self-heating chemicals 12 chemicals which, in contact with water, emit flammable gases 13 oxidizing liquids

where the employer can show that it is used in the workplace for the purpose intended by the chemical manufacturer or importer of the product, and the use results in a duration and frequency of exposure which is not greater than the range of exposures that could reasonably be experienced by consumers when used for the purpose intended;

	14 oxidizing solids 15 organic peroxides 16 corrosive to metals

or information on endpoints and other relevant data for the Clearinghouse. For example, the OSHA/GHS criteria (see table above) do not provide for distinguishing cardiotoxicity from neurotoxicity. The endpoints and other relevant data for these traits differ and will be important to include explicitly in the Clearinghouse. Further, the OSHA adaptation of GHS criteria is of limited value in specifying toxicological endpoints and provides no information on environmental endpoints.

The Hazard Traits described in the OEHHA regulation are more useful for identifying information that should be included in the Toxics Information Clearinghouse and provide for a level of detail that is lost by lumping all the organs together as "specific target organ toxicity."

ii. Use the OECD Harmonized Templates for Reporting Chemical Test Summaries and IUCLID framework.

Response: These templates are used for reporting chemical properties and human health effect studies required by various regulatory programs in Europe and in the US. They are responsive to the data requirements under the European REACH legislation. There are seven sets of OECD templates – on physico-chemical properties, degradation and accumulation, effects on biotic systems, health effects, analytical methods, and pesticide-residue chemistry. The templates do not provide toxicological, endpoints and other relevant data, so they are not useful for specifying the types of information to be included in the Clearinghouse. There also is a vast published literature that provides information on hazards with endpoints of importance that should be included in the Toxics Information Clearinghouse. While the format for the templates may be something for DTSC to consider in designing the Clearinghouse, the templates are too limited to be relied upon for meeting OEHHA's mandate under SB 509.

iii. Use US EPA's HERO database.

Response: US EPA has created an online searchable database that contains more than 300,000 articles from the peer-reviewed literature used to support the Integrated Risk Information System (IRIS). IRIS provides online health information on about 550 chemicals and the Integrated Science Assessment program that provides evaluations for six hazardous air contaminants. While this database can be extremely useful as a source of studies and data, it is not

> organized around chemical hazards. The hazard information can be obtained from US EPA's documents on the chemical. However, one must read the individual US EPA assessment documents to understand the endpoints and hazard traits for any given chemical. The database may be something for DTSC to consider as a valuable source of information, but it cannot be used as the basis for specifying hazard traits, toxicological and environmental endpoints and other relevant data that satisfies the requirements of OEHHA's SB 509 mandate.

Thus, none of the above suggested sources adequately meet the SB 509 mandate to specify hazard traits, endpoints, and other relevant data. However there is nothing in the regulation that excludes including the information available from the cited databases and systems in the Clearinghouse. For example, the Clearinghouse could provide electronic links to existing systems and search for relevant information in those systems. This also applies to the OECD chemical databases listed in Attachment I of the Koch comments.

There is nothing "non-standard" in OEHHA's approach to identifying information relevant to a chemical's toxicity for the Toxics Information Clearinghouse. As explained in the Initial Statement of Reasons, the definitions of hazard traits and toxicological and environmental endpoints are generally drawn or adapted from standard toxicological and ecotoxicological textbooks, federal guidance documents and international resources, such as the GHS and the World Health Organization. These are not "California-unique designations" of toxicities and endpoints. The regulation merely specifies the types of information to be included in the Clearinghouse and does not in any way exclude the use of existing information embedded in classification systems used for other purposes. No changes were made to the regulation based on these comments.

4. Comments on classifying chemicals or describing the evidence for hazard traits

Several comments expressed concern that the regulation is classifying chemicals and that OEHHA has gone beyond its authority by doing so.

GCA states:

> "The classification proposal should be abandoned entirely. SB 509 gives OEHHA neither the mandate nor the authority to create a novel California classification system. DTSC has responsibility for what actually gets placed into the TIC, not

> OEHHA. The classification system is a significant overstep of OEHHA's authority into DTSC's responsibilities."

Similar comments were reiterated in individual submissions by some of the signatories of the GCA comments (ACI, ACC, Amway Dow and P&G).

Similar comments were made on individual subsections of the regulation that describes "suggestive" and "strong" evidence (i.e., 69402.2, 69402.4, 69402.6, 69403.16, 69404.10) for example:

> "This entire section is unnecessary and unauthorized by the statute (SB 509) in that the office is attempting to classify chemicals when it is only authorized to specify hazard traits and endpoints…" (GCA, ACI)

Other related comments were made:

> "The OEHHA proposes a California–only system where hazard information for a given substance is classified as either strong or suggestive evidence for assigning a hazard trait." (Dow)

> "It is important to note that DTSC, in its Toxics Information Clearinghouse Feasibility Study Report, suggests that the user will make their own judgment as to the hazards, based on the information presented" (GCA)

> The "Hazard Trait Regulation and Clearinghouse should be open to including all information available on a chemical, but remain as objective as possible, without introducing biases and subjectivity through a classification system." (GCA, P&G)

Another comment confused OEHHA's regulation and the earlier proposal by DTSC (under AB 1879):

> "The proposed SCPA rule explicitly states that a hazard trait "can be demonstrated by suggestive evidence…The proposal will encourage reliance on such limited data, even in the absence of more probative studies." (NAIMA)

Others saw the utility in these sections. For example, CDPH writes:

> "The sections of the regulations defining "strong evidence" or "suggestive evidence" for each hazard trait provide clear, scientifically-based guidance that will be helpful for anyone involved in evaluating the vast amount of information

that exists on chemicals and their effects. The inclusion of hazard indicators such as those based on structure-activity relationships or mechanistic evidence from cell- or tissue-based assays, reflects the use of current scientific knowledge of chemical hazards."

Response: The regulation does not classify chemicals. The regulation identifies, for inclusion in the Clearinghouse, hazard traits and the scientific information that may be available for a chemical regarding a hazard trait. As discussed in response to Comment 3, DTSC is responsible for developing criteria by which chemicals and their alternatives may be evaluated. DTSC will make its own decisions regarding the assigning of hazard traits to specific chemicals, the identification of chemicals of concern.

The regulation also provides general guidance that describes the type of information that represents strong or suggestive evidence of a hazard trait. Some chemicals have a large and robust database, while for others there is little information available. This is very common when reviewing hazard information for a chemical. Some types of information may provide more complete evidence regarding a hazard trait, while other types of information may provide only partial evidence. For example, an authoritative organization may have comprehensively reviewed available evidence and concluded a given chemical is carcinogenic. This would be considered strong evidence of carcinogenicity. Alternatively, an authoritative organization may have concluded there is limited evidence for carcinogenicity of a given chemical. This would be considered suggestive evidence.

The discussion of strong and suggestive evidence in the regulation falls within the authority provided to OEHHA by SB 509 because OEHHA has the responsibility to both evaluate and specify hazard traits, end-points and other relevant data. It is appropriate and necessary to provide this guidance to help DTSC, product manufacturers, non-governmental organizations and other users of the Clearinghouse to have a better understanding of the information in the Clearinghouse relating to a given chemical and its possible hazard traits. Without this guidance all the scientific evidence in the Clearinghouse could be viewed as equally strong or weak when that is not the case.

No changes were made to the regulation based on these comments.

5. Comments on the weight and degree of evidence for hazard traits.

5a. Comment: GCA commented that there is no weight-of-the-evidence approach in the regulation that could be used to evaluate data and assign hazard traits to chemicals. Similar comments regarding lack of a weight-of-evidence approach in the regulation were submitted by PCPC, P&G, RMA, and Dow. As an example,

> "It is a general principle of hazard assessment that all available data must be considered and the totality of relevant and reliable information integrated in order to arrive at a scientifically defensible decision regarding chemical hazard…the only valid scientific approach is to consider the weight of the scientific evidence. …specific discussion of how a weight-of-the-evidence assessment should be, and will be, performed is needed."

Dow and Koch note a need to consider both positive and negative data on a chemical.

RMA's comments generally focused on their view that the regulation "lowers the level and strength of evidence that can be used to classify a substance as having a hazard trait." They express concern that the regulations "systematically change the current risk-based product regulatory framework into a hazard-based product regulatory framework".

Concerning the strong evidence descriptions in 69402.4 and 69402.6, Dow writes "As written, most of these criteria do not take exposure into account" and are hazard-based. Dow suggests that the regulation include provisions for critically evaluating information.

A Dow comment on suggestive evidence expresses concern that the suggestive evidence for developmental toxicity and reproductive toxicity will be used for "classification by association without direct evidence of developmental toxicity."

Response: The concern expressed in these and similar comments arises in part from confusion over the purpose of Sections 69402.2, 69402.4, 69402.6, 69403.17 and 69404.10 of OEHHA's regulations, which describe general levels of evidence for the hazard traits. It is widely recognized that the information available on industrial chemicals that end up in consumer products ranges from nothing to very substantial. The sections describing levels of evidence in the regulation are general guidance to those who may use the information in the Clearinghouse, including DTSC, businesses, and the general public. The response to Comment 4 includes an expanded discussion of this guidance.

The regulation does not define a process, such as a weight-of-the-evidence approach, or criteria for DTSC to prioritize chemicals of concern or to make regulatory decisions on chemicals in consumer products. DTSC is responsible for defining any weight-of-the-evidence approach that it might use in assigning hazard traits to chemicals, identifying and prioritizing chemicals of concern, and making regulatory decisions on chemicals in consumer products. OEHHA would be exceeding its authority under SB

509 if it were to define a weight-of-the-evidence approach instead of deferring to DTSC on this issue.

The OEHHA regulation does not change a risk-based regulatory framework into a hazard-based regulatory framework because it only specifies the types of information that need to be included in the Clearinghouse, not how one uses the information in a regulatory context. The regulation does not restrict DTSC to only considering specific types of information when prioritizing chemicals or conducting alternatives assessments.

OEHHA recognizes that the available scientific information has to be viewed in the overall context of the available relevant information on a specific chemical in deciding whether or not a chemical has a hazard trait. OEHHA reworded the regulation to respond to this and other related comments. For "other toxicological" and environmental hazard traits (subsections 69403.17 and 69404.10), where there are fewer authoritative organizations making general findings about the presence of the trait, the regulation now provides that available data from well-conducted scientific studies may be considered either strong or suggestive evidence. For toxicities where there has been more focus (i.e., carcinogenicity, reproductive toxicity, developmental toxicity) an authoritative body will have already applied a weight-of-evidence analysis conducted in the context of the database as a whole for many chemicals. Thus, the wording of the types of information indicating strong and suggestive evidence for these three endpoints (Subsections 69402.2, 69402.4, and 69402.6) is different than for other toxicological hazard traits and environmental hazard traits (subsections 69403.17 and 69404.10), reflecting the existence of a number of authoritative organizations that have evaluated carcinogenicity and reproductive and developmental toxicity. No other changes were made to the regulation based on these comments.

5b. Comment: RMA notes that the proposed regulation "defines suggestive evidence as including evidence from (a) a single experiment; (b) where design, conduct or interpretation of the studies may be questionable; (c) that the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) that is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs."

Response: The quote in the comment is not contained in the regulation. Rather, the comment is paraphrasing a quote in the ISOR, page 92, from the International Agency for Research on Cancer's (IARC) criteria for suggestive evidence of carcinogenicity. IARC is a well-established authoritative body whose purpose is to evaluate evidence on whether a chemical is carcinogenic, and classify chemicals as to carcinogenicity. IARC

was quoted in the ISOR to provide an example of an authoritative organization's thinking to explain the meaning of suggestive evidence. In the ISOR, OEHHA explains its rationale for Subsection 69403.16 (now 69403.17) that describes the types of evidence that constitute suggestive evidence. No changes were made to the regulation based on this comment.

5c. Comment: RMA writes: "The proposed rule allows DTSC to classify a substance as having a hazard trait merely due to a chemical or physical property." The comment cites an example of a chemical being strongly electrophilic.

Response: As explained in the ISOR, strongly electrophilic chemicals bind to cellular macromolecules and this binding can result in dysfunction across a wide array of cellular functions. Thus, it is justifiable to consider studies indicating strong electrophilicity as evidence of the hazard trait "Reactivity in Biological Systems." Toxicological endpoints for this trait emphasize in vivo observations of reactivity in biological systems, such as covalent binding to macromolecules. The regulation does not require DTSC to classify a substance as having any particular hazard trait. No changes were made to the regulation based on this comment.

5d. Comment: RMA writes: "This approach contemplates that a substance might be given a hazard trait even if there was neither strong nor suggestive evidence," citing the ISOR, and goes on to a lengthy explanation regarding why this approach is inappropriate. "The approach in the regulation ignores causation, including description of some of the Hill criteria for causality used in the field of epidemiology." RMA spends considerable text describing the criteria for causality.

Response: It is incorrect that the approach promotes the assignment of a hazard trait in the absence of strong or suggestive evidence. The regulation does not provide advice indicating that a hazard trait should be assigned in the absence of evidence. See also response to comment 7 below. The discussion in the ISOR was explaining that where there is not information on a chemical we do not know one way or the other whether it has a hazard trait.

With regard to the Bradford-Hill criteria, these are used to evaluate epidemiological studies. As noted by Sir Bradford-Hill himself, the Hill criteria for causality are guidelines, not requirements, for deciding a substance causes a disease in humans. Finally, this regulation is responding to the mandate set out by SB 509, not AB 1879. It is DTSC pursuant to AB 1879 that decides the specific criteria by which chemicals and their alternatives may be evaluated. No changes were made to the regulation based on this comment.

6. Comment on format of information in the Clearinghouse

Dow expressed concern that all substances are likely to have a hazard trait, and the Clearinghouse needs to contain information that allows DTSC to assess relative hazards between substances.

Dow further states that the purpose of the Clearinghouse dictates the architecture, data format and information requirements. Key elements for the prioritization process and alternatives assessment (relative hazards posed by chemicals) should be built into the Clearinghouse.

Response: OEHHA agrees that other factors are important to the prioritization and alternatives assessment processes besides the hazard traits. The Toxics Information Clearinghouse is meant to be a repository of information about the hazards of chemicals in consumer products. As required by SB 509, DTSC will develop the architecture and data format requirements for the Clearinghouse. OEHHA's role is to specify the hazard traits, endpoints and other relevant data to be included in the Clearinghouse. This and other similar comments regarding how the Clearinghouse should be structured are not relevant to this regulation, but are relevant to DTSC's regulatory process.
Finally, regarding integrating information to prioritize chemicals, AB 1879 directs DTSC to develop a process for that information for a number of factors, including but not limited to information in the Clearinghouse. (Health and Safety Code Section 25252)

No changes were made to the regulation based on this comment.

7. Comments on chemicals that have no data

Some comments called for indicating in the Clearinghouse when a chemical has no data on a hazard trait.

> "One area that needs additional attention would be to distinguish between cases where data were available to suggest that a chemical did not have a hazard trait and cases where data were not available at all. At present, the proposal appears to treat "no data" the same as "no hazard." There is a tendency to treat chemicals with no data the same as those with no problem. The approach needs to clearly distinguish between these cases." (Dr. Kyle)

> "For chemicals that are unstudied or under-studied, the TIC should ensure the inclusion of a data field that indicates the chemical has not been sufficiently examined to make a determination. As we know absence of data is not the same as absence of harm…" (CHANGE)
>
> "Make it explicitly clear when a lack of hazard data is the result of limited or no research on a particular chemical, to prevent the inference that such a chemical is safe. (CWA)

Response: OEHHA agrees that absence of evidence is not evidence of absence of effect. However, this regulation identifies what types of data should be in the Clearinghouse, and does not establish the eventual format of the Clearinghouse. This regulation does not assign hazard traits to chemicals, or classify chemicals as to hazard. Thus it does not treat "no data" as "no hazard".

These comments are of relevance to DTSC, which is responsible for constructing the Clearinghouse. However, these comments are not relevant to this regulation. No changes were made to the regulation based on this comment.

8. Comments on including information from newer/alternative testing methods

Some comments supported the regulation's inclusion of information from newer toxicity testing paradigms in the Clearinghouse.

> "It is crucial for protection of public health and the environment that the criteria used to evaluate a chemical's safety, do not rely on outdated scientific methods that were relied upon over the past 40 years. OEHHA's proposal is the most scientifically up to date criteria established and is consistent with the recommendations of the National Academy of Sciences which has called for looking for more "upstream" at early indicators of harm utilizing more advanced scientific methods. OEHHA's proposal is flexible and will allow for the incorporation of newer and rapidly evolving toxicity testing methods which can address multiple hazard traits." (NRDC and EWG)
>
> "OEHHA is to be commended for aligning the orientation of its draft rulemaking with important recommendations from the National Academy of Sciences. It is an imperative to update toxicity testing methods to reflect current science." (CHANGE)

> "the explicit use of evidence from *ex vivo*, *in vitro*, and non-animal tests is welcome as forward-looking policy. Regulatory agencies from Health Canada to the European Chemicals Agency are investigating ways in which they can use this information to improve substance assessments and we applaud CalEPA for its leadership in this area." (PCRM)

Dow supported the inclusion of data from alternative methods, but with some limitations on its use in identifying hazard traits:

> *"Where data gaps are identified*, it is generally accepted that the development and use of methods limiting or replacing the use of animals in some toxicity evaluations will be necessary in future hazard assessment programs. …We actively support the development and use of alternative test methods that are scientifically credible and acceptable as long as the limitations of the test method are clearly acknowledged (i.e. preliminary screening method). In these instances, data from these test methods alone are insufficient to conclude that the chemical has that hazard trait."

Dow also suggested amending the regulation to convey how the information would be used in evaluating a chemical.

> "*Where data from multiple test methods already exist* for a chemical, the use of data derived from alternative test methods in the evaluation of a substance Hazard Trait needs to take into account its intended application. … In the case where the alternative test method is a preliminary screening assessment (e.g. computer-based structure-activity databases, physical property evaluations, preliminary exposure assessments, in vitro assays and short-term toxicity screens involving small numbers of animals) AND higher tiered *in vivo* animal data are available, results of data from higher-tiered *in vivo* animal studies should supersede the results from preliminary screening assessment studies."…

Response: Comments noted. This regulation identifies toxicological and environmental endpoints and other relevant data that include all types of information relevant for evaluating hazard traits, not just information generated by the older traditional toxicity testing paradigms. In regard to the concern about the use of alternative test results in a decision on whether or not a chemical exhibits a hazard trait, the regulation does not make determinations about whether a given chemical does or does not have a hazard trait. Those determinations are made by DTSC. However, in this regard, it is important to note that alternative test information can clarify or complement the findings of traditional animal studies and epidemiology. In some cases the alternative data may

show an effect in an older study to be irrelevant, and in other cases the study may provide further support or new insights. No changes were made to the regulation based on these comments.

9. Comments on use of *in vitro* and structure-activity data

Varied comments were received concerning *in vitro* studies and structure activity data, including from Quantitative Structure Activity Relationship models. GCA writes that these assays and models are:

> "…generally recognized as appropriate tools prioritizing chemicals and identifying the need for more complex biological system testing, but are limited in their ability by themselves to make decisions about risk or even classification of toxicological properties as OEHHA proposes …All testing methods in the proposed regulation should be based on national and international standard protocols or validation by an appropriate authoritative body."

Similar concerns were expressed by ACC:

> "The conclusive identification of a toxicity hazard trait based solely on data obtained using *in vitro* methods or structural/predictive models is not scientifically justified. It is broadly recognized that the science of many *in vitro* screening assays has not advanced to the level of assuring that *in vitro* results are predictive of *in vivo* activity or can be considered to be robust measures of toxicity hazard. … The use of *in vitro or in silico* data as the *sole basis* for concluding that a chemical possesses a hazard trait is over reaching and should be removed from the OEHHA Proposal. While it is entirely appropriate to include information from *in vitro* studies and structure-activity models (as well as read across, expert judgment) in a WOE evaluation, it is not appropriate to draw conclusions about hazard from these sources alone…Further, OEHHA needs to clearly identify how certain types of data, such as *in vitro* data, should be weighted when assessing chemical hazards, recognizing that some types of data are less reliable and less predictive of apical effects than others."

On the other hand, PCRM called for inclusion and use of both structure activity and in vitro evidence, noting limitations of animal studies:

> "Substances that have no effects in a select animal 'model' are not necessarily safe, and vice versa. The regulation also consistently places (Q)SAR and *in vitro* approaches into the 'other evidence/suggestive evidence' category (with the

> exception of genotoxicity), implying that this evidence should be weighed less heavily than evidence from animal tests. In fact, models are more easily accepted for certain hazard endpoints over others, and this should be reflected in the regulation. For example, (Q)SAR models have been used for decades by the US EPA to estimate acute fish toxicity. The results of certain models are considered more acceptable than others. Also within the (Q)SAR field, applicability domain matters. In the past, users of (Q)SAR models did not pay enough attention to the kinds of substances the model was designed to be used for, and so the predictions they obtained were poor."

Also, although it was already included as other relevant data for the toxicological and environmental hazard traits in the regulation, PCRM called for the introduction of a type of structure activity data:

> "An endpoint OEHHA should consider introducing into the regulation is a 'structural alert,' which refers to particular moieties of a substance's structure that indicate the potential for a toxic endpoint."

RMA also expressed concern about using structure-activity relationships as evidence of a hazard trait. They cite for this concern that in the Initial Statement of Reasons (ISOR) OEHHA discusses the structure activity modeling from EPA's program Oncologic as an example of suggestive evidence.

Response: This regulation establishes the types of data that should be included in the Clearinghouse, which is a repository of information. The regulation specifies that structure activity and in vitro data are to be included. DTSC will determine how to use the information in the Clearinghouse and make decisions about whether a chemical does or does not have a hazard trait. While the regulation does not classify chemicals, it does provide general guidance on whether there is suggestive or strong evidence that a chemical exhibits a hazard trait, and it indicates that structure activity and in vitro data can provide suggestive evidence for several hazard traits.

The QSAR program Oncologic has been used for decades by US EPA in their new chemicals screening to evaluate potential for carcinogenicity, and there are other models being used and developed by academia, industry and government for a variety of hazard traits. The reliability of any QSAR prediction will depend on many factors, including the data used in developing the QSAR model, as indicated by one of the comments. Results from QSAR models like Oncologic may provide suggestive evidence, depending on the chemical and the appropriateness of the particular model for that chemical.

OEHHA agrees that structural alert information could also be useful in evaluating a chemical, and the regulation also provides for the inclusion of this information *In vitro* and *in silico* information can provide important evidence for evaluating the toxicity of a chemical. That is why the regulation includes this type of information as other relevant data for toxicological hazard traits. This regulation does not require anyone to assign a hazard trait to a given chemical based on structure activity relationship or mechanistic in vitro data; it simply identifies those data that should be available in the Clearinghouse so they can be part of the information available on a chemical's potential toxicity.

Study validation is outside the scope of this regulation. Pursuant to SB 509, DTSC has the mandate for data quality for the Clearinghouse. No changes were made to the regulation based on these comments.

10. Comments on potency of chemicals as important to evaluating hazard and risk

GCA expressed concern that the regulation does not address the issue of potency of a chemical to induce an adverse effect. They comment that:

> "…potency is a measure of the hazard potential and is a critical part of any hazard identification process…OEHHA has established a framework that will undoubtedly be misunderstood and certainly misused. We recommend that OEHHA look at existing systems, particularly the OECD Harmonized Templates for Reporting Chemical Test Summaries… to understand how authoritative and respected bodies have handled this critical issue." (GCA)

Similar comments are made by other signatories to the GCA comments (ACC, Amway, PCPC, P&G) and RMA.

Dow questions where DTSC will get the information on dose-response data used in assigning a hazard trait.

> "Will DTSC be required to conduct a separate review of the hazard data in order to obtain this information? If so, this would be a tremendous waste of time and resources when OEHHA will be reviewing these data to assign hazard traits and could include such information at the time of its assessment."

Response: OEHHA disagrees that potency is a part of any hazard identification process. For example, the International Agency for Research on Cancer, the US Environmental Protection Agency and the National Toxicology Program, pre-eminent organizations in the identification of carcinogens, do not typically include potency as part of their carcinogen identification processes. Potency is therefore not included in the part of the regulation specifying hazard traits, endpoints and other relevant data related to these hazard traits.

OEHHA recognizes the importance of considering the potency of a toxic chemical when evaluating risk from exposure. Such analyses are a major component of OEHHA's other mandated work regarding chemical risk assessment. Exposure-response information, which is indicative of a toxic chemical's potency, can be useful to DTSC in prioritizing chemicals and in alternatives assessment. Because potency and other exposure-response information can be important in prioritization and alternatives assessment, based on these and other comments, a new Article 7 "Additional Relevant Data" was added to the regulation that specifically includes exposure-response information.

11. Comments on data quality/reliability criteria

A number of comments were made concerning data quality in the regulation. GCA states:

> "OEHHA needs to clearly identify how certain types of data should be weighed when assessing chemical hazards, recognizing that certain types of data are less appropriate than others, even if they are developed by authoritative bodies."

GCA goes on to ask for quality control and guidance for data quality, noting that:

> "…data quality and weighting considerations are critical in ensuring good decision making in Prioritization and Alternative Analysis…OEHHA together with DTSC should adopt the robust study summary format used in the OECD's hazard assessment program and OECD harmonized templates as a model for populating the TIC…"

Similar concerns were expressed by other signatories to the GCA comments (ACC, P&G, Dow, Dupont, GMA, Koch), and NAIMA.

> "[Koch] recommends that OEHHA incorporate a data quality system to verify the reliability and utility of the data selected for the TIC, and develop a proposal for

> periodically updating the information. OEHHA's process should include review of the data and other information available, updating where needed, removal of old or discredited information, elimination of duplication, and where possible confirming the accuracy and credibility of information."

Dow suggests utilizing a Klimisch scoring system:

> "Klimisch *et al* (1997) developed a scoring system to assess the reliability of data, particularly from toxicological and ecotoxicological studies… This system built upon existing guidance produced by the European Commission (EU 19942, 19953) and the considerations on the assessment of the quality of data used today in the US and OECD HPV programme (OECD 19944)"

Dupont connects "well-conducted studies" mentioned in the regulations with ensuring good data quality and comments that the well-conducted studies should be required to provide references when attributing information from another source.

Response: These comments address the issue of data quality, an important consideration. However, they are not relevant to this particular regulation which specifies types of hazard traits, endpoints and other relevant data that should be included in the Toxics Information Clearinghouse as required by SB 509, in subsection 25256.1 of the Health and Safety Code. Another provision of the statute – HSC Section 25256(2)(a) -- gives responsibilities to DTSC to determine data quality requirements and standards for the Clearinghouse.

No changes were made to the regulation based on these comments.

12. Comments on need for independent scientific peer review

ACC and GCA noted the need for independent scientific peer review of the regulation.

> "The scientific portions of the proposed regulation have not yet been subjected to independent external scientific peer review. Under California Health and Safety Code Section 57004 (HSC 57004), all CalEPA organizations, including OEHHA, are required to conduct an external scientific peer review of the scientific basis for any rule proposed for adoption, and a final regulation cannot be issued until such a scientific peer review has been completed." (GCA)

Response: The regulation and Initial Statement of Reason have undergone scientific peer review through the University of California, pursuant to Health and Safety Code

Section 57004. The peer reviewer comments are discussed in a separate section of this response to comments. No changes were made to the regulation based on this comment.

13. Comment on nanomaterials in the regulation

The nanotechnology industry trade organization commented on portions of the regulation relevant to nano-sized materials. CalNIN writes:

> "It is OEHHA's view that the potential for hazard traits associated with certain nanomaterials is appropriately addressed in the Proposed Regulation. While nanomaterials share a common property of being at the nano scale, the term is applied to an increasingly broad range of materials that possess an extraordinary array of properties and which may exist in a broad range of matrices. Given this, nanomaterials fit into this Proposed Scheme just as other chemicals do: depending upon the traits that the specific material actually exhibits."

Response: Comment noted. We agree that nanomaterials vary widely in their characteristics and that the hazard traits of nanomaterials would need to be evaluated for each specific nanomaterial. No changes were made to the regulation based on this comment.

14. Comment on Impact of regulation on recycling

One commenter expressed concern that the Green Chemistry Initiative could impact the ability to recycle post-consumer materials. MBA Polymers writes:

> "As a world-leading recycler, we want to make sure that the good intentions of this initiative don't KILL RECYCLING. Recyclers have to deal with small amounts of many different legacy chemicals/additives in the materials they recover from end of life electronics, appliances, computers and automobiles….We sort out the plastics containing these legacy additives from the plastics that don't – but no separation process is perfect, so small amounts of plastics containing these legacy additives remain in our products…Our company wants to make sure that the Green Chemistry regulations also recognize the enormous benefits from recycling … don't kill recycling by setting "zero" standards for substances of concern."

Response: The regulation does not set any standards for any chemicals; therefore, this comment is not relevant to this rulemaking. No changes were made to the regulation based on this comment.

Comments on Article 1

15. Comments on section 69401 Purpose and Applicability

15a. Comment: Koch writes:

> "The Purpose and Applicability section of the Proposed Regulation (Section 69401) fails to outline the scope of chemicals and chemical information that will be available on the TIC. The applicability section should identify the universe of chemicals that will be included, how the chemical information will be identified and who will decide what is appropriate for inclusion. If OEHHA intends a phased-in approach, the Proposed Regulations should state so clearly. KII also recommends referencing how the chemicals under consideration contemplated in Health and Safety Code Section 25252 will be incorporated or prioritized…"

Response: SB 509 requires OEHHA to specify the hazard traits, endpoints and other relevant data that should be included in the Clearinghouse. DTSC is tasked with the duties identified in this comment, and the issues raised are for DTSC's rulemaking process. No changes were made to the regulation based on this comment.

15b. Comment: NAMC recommends that the following text be added in Article 1 General; § 69401, Purpose and Applicability:

> "Metals and metal substances are different from organic chemicals. The potential hazard of a metal depends on the specific metal, the form of the metal and/or metal compound, and the organism's ability to regulate and/or store the metal. Certain traits used to screen, assess, or prioritize organic compounds, such as bioaccumulation and persistence, are not appropriate for assessing the hazard of metals. For more information on how to assess metals and metal substances, please refer to the U.S. Environmental Protection Agency's (EPA) *Framework for Metals Risk Assessment*."

Response: OEHHA appreciates that the toxicity of a metal compound is dependent on a number of factors including solubility in biological fluids, homeostatic mechanisms, and pharmacokinetics. However, the suggested language is not appropriate for this

regulation, which does not define or classify hazard traits for specific substances. Further, the hazard traits named - bioaccumulation and persistence - can be very important for metals, as is well recognized for lead and cadmium, which are both toxic and bioaccumulative. The nuances of the toxicity of metal compounds will need to be evaluated during the prioritization and alternatives assessments processes. These processes are not the subject of this regulation. No changes were made to the regulation based on this comment.

16. Comment on section 69401.2 – Definitions

16a. Comment on (a) "adverse effect"

RMA comments that OEHHA's definition of adverse effect is not the same as the National Research Council 2007 report's definition of a biological response or the American Society for Veterinary Clinical Pathology's definition of adverse. Both reports are cited in the ISOR.

Response: RMA appears to misunderstand the ISOR discussion on this point. The definition of adverse effect for toxicological endpoints in the regulation is taken verbatim from the U.S. Environmental Protection Agency, as noted in the ISOR. The quote in the ISOR from the National Research Council Toxicity Testing in the 21st Century: A Vision and Strategy is wholly consistent with the U.S.EPA definition of adverse effect. The ISOR states:

> "The National Research Council report states that:
>
> > 'Biologic responses are viewed as results of an intersection of exposure and biologic function. The intersection results in perturbation of biologic pathways. When perturbations are sufficiently large or when the host is unable to adapt because of underlying nutritional, genetic, disease or life-stage status biologic function is compromised, and this leads to toxicity and disease.'
>
> "Using the definition in the proposed regulation, any perturbation that would lead to toxicity and disease would be considered "adverse." Perturbations that would not lead to toxicity would not be considered adverse."

This is not inconsistent with the definition of adverse effect in the regulation:

> " "Adverse effect" for toxicological hazard traits and endpoints means a biochemical change, functional impairment, or pathologic lesion that negatively affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge."

Similarly, the ISOR states:

> "The definition in the proposed regulation is also consistent with the definition of "adverse" adopted by the American Society for Veterinary Clinical Pathology:
>
> > "Adverse. A biochemical, morphological, or physiological change (in response to a stimuli) that either singly or in combination adversely affects the performance of the whole organism or reduces the organism's ability to respond to an additional environmental challenge."

Again, it is unclear (and the comment does not describe) how this is inconsistent with the definition of adverse effects in the regulation. No changes were made to the regulation based on this comment.

16b. Comments on (b) "Authoritative organization"

Comment: "This definition fails to account for the concept of "deliberative review" in coming up with scientific findings versus creation of derivative lists. Referencing "other states" is particularly concerning, where there are generally no authoritative processes in place. However, on page 4 (of 24) the wording suggests that "authoritative organizations" are limited to those listed." (GCA, ACC, ACI)

Response: A minor change to the wording of the regulation was made to address this concern. In Subsection 69401.2 (b)(4), we added environmental and public health regulatory agencies of other states as authoritative organizations. Such entities would have regulatory processes in place. However, the authoritative organizations list in section 69401.2 was meant to be inclusive, not exclusive.

Comment: CDPH writes Section "69401.2(b)(1) recognizes OEHHA, DTSC, and other California departments and agencies as "authoritative organizations." This is appropriate and may encourage inter-agency cooperation in controlling hazardous chemicals. We suggest adding an "including but not limited to" list that specifically names CDPH, Cal/OSHA, and perhaps some departments related to wildlife (Fish and Game, Natural Resources). Explicit inclusion within regulatory language can remind agencies who they should be communicating and collaborating with."

Response: Section 69401.2 (b) (1) includes other State of California Boards, Departments, Offices or Agencies as authoritative organizations. Thus, CDPH, Cal/OSHA, Department of Fish and Game and Resources Agency are all authoritative organizations. Calling out certain state entities could be confusing and is unnecessary.

No changes were made to the regulation based on this comment.

Comment: CDPH writes: "69401.2(b)(3) should be corrected to read "National Institute **for** Occupational Safety and Health."

Response: The correction was made and the regulation changed to address this comment.

16c. Comments on (c) "Chemical substance"

"This definition is broadly expansive and different from DTSC's proposal." (GCA, ACC)

Response: The definition in the regulation is consistent with the substance of the original DTSC proposed regulation. To accomplish the intent of SB 509 and AB 1879, the Clearinghouse should include information on any chemical substance, including chemical mixtures, and chemical metabolites and degradation products that might result from use of a chemical in a consumer product. Thus the regulation's definition of chemical substance includes metabolites and degradation products in this section, so that the full phrase "including chemical mixtures, and chemical metabolites and degradation products" does not have to be repeated for each of the definitions of hazard trait where the term "chemical substance" is used. No changes were made to the regulation based on this comment.

16d. Comments on (e) "Hazard Traits"

"[T]his definition lacks clarity in that it does not actually define what a hazard trait is, but states (in a circular fashion) the types of hazards. Hazards are, in the context of chemicals, inherent properties that lead to adverse effects in humans and wildlife. In the context of the present regulation, they are toxicities." (GCA)

"It should be clearly stated in the definition of "hazard traits" that it is an inherent property that leads to adverse effects in humans or wildlife." (ACI).

Response: While OEHHA disagrees that the definition of hazard trait is circular, OEHHA amended the definition to read:

> "Hazard traits are properties of chemicals that fall into broad categories of toxicological, environmental, exposure potential and physical hazards that may contribute to adverse effects in exposed humans, wildlife, or in ecological communities, population or ecosystems."

16e. Comment:

> "The proposed rule so broadly defines hazard traits that it substantially lowers the level and strength of evidence that can be used by the Department of Toxic Substances Control ("DTSC") to classify a substance." (NAIMA)

A similar comment was made by RMA.

RMA also comments that "the hazard trait selection process has few or no checks and balances on the discretion of DTSC in determining whether a substance or product possesses a hazard trait."

Response: The definition of hazard trait is separate from the processes that DTSC may use to classify chemicals or assign hazard traits to specific chemicals. This regulation defines the types of information that are to be included in the Clearinghouse. This regulation does not establish criteria for classifying chemicals or establish a hazard trait selection process. DTSC can use the information in the Clearinghouse as well as any other information it determines is pertinent in deciding whether a chemical has or does not have a hazard trait. Comments concerning the criteria used to definitively assign a specific hazard trait to a chemical should be addressed in the DTSC regulatory process and are not relevant to this regulation. No changes were made to the regulation based on this comment.

16f. Comments on (f) "Mechanistic similarity"

> "[T]his definition is sweeping and imprecise and is not consistent with the terms usually applied within the toxicological community. This definition should be expanded to include not only a similar mode of action/toxicological effect, but also considerations of the toxicokinetic profile of the chemical (such as in their absorption, distribution, metabolism, and excretion (ADME) profile, for example, or in their Physiologically-based, Pharmacokinetic (PBPK) models). The

> toxicokinetic profile is important to establish whether the same level of concern is warranted for a chemical with a similar mode of action." (GCA, ACC)

Response: The regulation provides a general definition for mechanistic similarity to encompass the variety of ways chemicals can be mechanistically similar and produce toxicological effects. OEHHA disagrees that the definition is sweeping and imprecise. The degree of generality in the regulation is intentional.

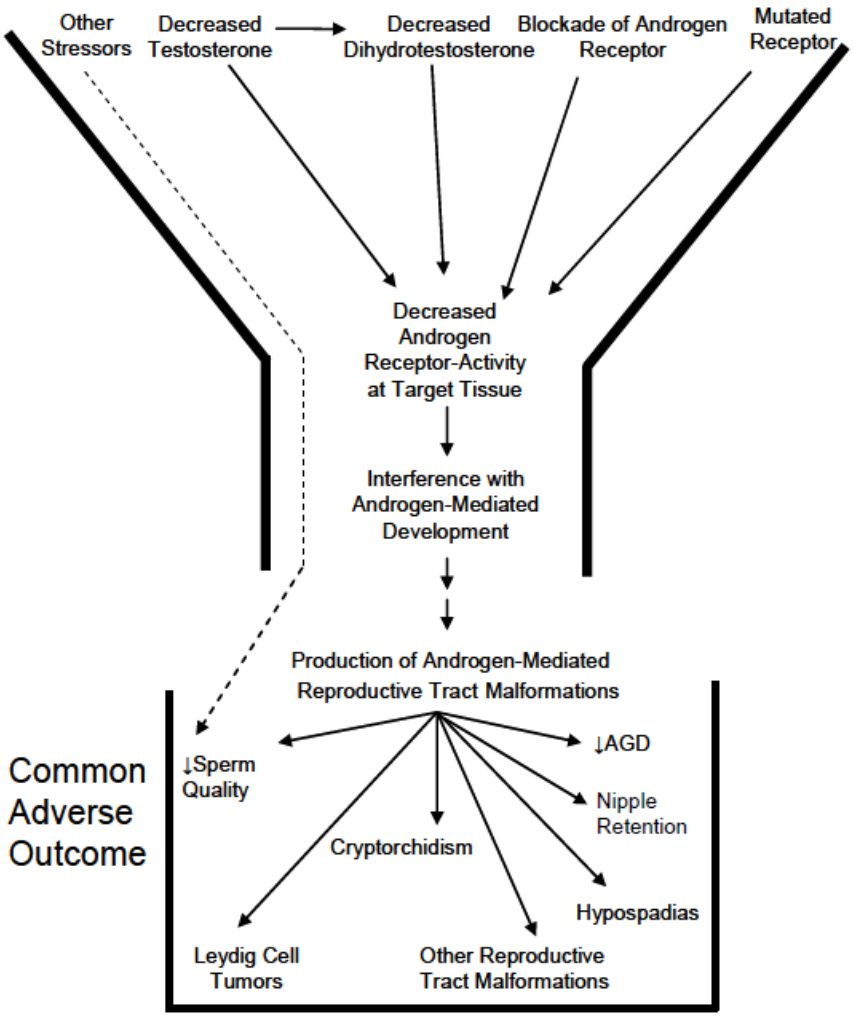
By way of example, interference with the action of testosterone or blockage of the androgen receptor resulting in significant androgen insufficiency in the developing fetus would be expected to result in many of the male reproductive system malformations caused by the class of chemicals known as phthalates, as pointed out in the ISOR, referencing the National Academy of Sciences (NAS) 2008 report "Phthalates and Cumulative Risk Assessment" (ISOR, page 48). Chemicals that cause significant androgen insufficiency by interfering with the action of testosterone or blocking the androgen receptor would be considered mechanistically similar to phthalates. The developmental toxicity that results from the androgen insufficiency caused by phthalates is well established. If another chemical also causes significant androgen insufficiency, it would also be expected to cause developmental toxicity via the developing fetus.

The regulation in subsection 69402.3 (c) includes as "other relevant data" for developmental toxicity "mechanistic similarity to other chemical substances that are toxic to developing organisms." Thus data on a chemical's ability to cause androgen insufficiency would be included in the Clearinghouse. The comments call for expanding the definition in two ways. The first is to include "similar mode of action/toxicological effect" in the definition. The second is to include considerations of the toxicokinetic profile, such as ADME or as indicated in a PBPK model.

The 2007 NAS report Toxicity Testing in the 21st Century (page 38) provides a general definition for the term "mode of action":

> "Mode of action. A description of key events or processes by which an agent causes a disease state or other adverse effect."

This term was not included in the regulation because it could potentially lead to confusion. The example of androgen insufficiency will be used to explain why. The figure below illustrates the adverse developmental effects, such as undescended testes, that can occur when the rat fetus is exposed to various chemicals that cause androgen insufficiency. This figure was taken from the NAS report "Phthalates and Cumulative Risk Assessment," which is cited in the ISOR.



As noted above, mode of action refers to the processes or key events by which a chemical causes the effect. For phthalates a key early event is decreased testosterone. This decrease in testosterone precedes a series of effects in the fetal testis. (There are also a series of key steps that precede testosterone reduction by phthalates.) Other, non-phthalate chemicals can also cause androgen insufficiency and the resulting testicular effects seen with fetal exposure but the early key events in the process can be different, For example, some chemicals can cause the same effects by blocking the androgen receptor. As noted by the NAS in the phthalate report:

> "The overall spectrum of induced malformations resulting from disturbances in androgen concentration is very similar to that resulting from disturbances in signaling. Although there might be quantitative differences in the individual malformations produced, depending on precise mechanisms or doses, the similarity in response of the androgen-dependent organs indicates that few

> independent pathways of response exist in relation to androgen disturbances. Thus, a developing prostate seems to respond in the same manner irrespective of the agent that lowers the concentration of a ligand, whether testosterone or DHT, or that blocks or alters signaling of the AR in the target tissue. Accordingly, the prostatic malformations induced by phthalates (which lower fetal testicular testosterone production), AR antagonists (such as flutamide and vinclozolin), mixed acting agents (such as prochloraz), and the 5α-reductase inhibitor finasteride are identical." (NAS, 2008, Phthalates and Cumulative Risk Assessment, page 55).

The major key event, decrease in androgen sufficiency, and subsequent male reproductive toxicity outcomes is similar across chemicals. Under the definition in the regulation they would be "mechanistically similar." Under a definition that required the same mode of action across chemicals, they would not be "mechanistically similar" because early key events differ.

The comment also suggests including considerations of the toxicokinetic profile of the chemical in the definition of mechanistic similarity. We agree that toxicokinetics plays an important role in the ultimate response to a chemical following exposure or intake, and may play a role in evaluating whether or not a chemical can, for example, be metabolized to a specific moiety that may be active. But the broader descriptions of how a chemical moves through an organism using, for example, a PBPK model is not what is envisioned for "other relevant data" for specific toxicological hazard traits. Data to support a PBPK model of the chemical would fall outside "other relevant data" specific to the hazard trait. As noted in the comment, the toxicokinetics of a compound can raise or lower the overall level of concern about a chemical, but that is more relevant to prioritization of chemicals than it is to "other relevant data" for hazard traits in the Clearinghouse. As noted in the example above, chemicals with different toxicokinetic characteristics may ultimately share a similar mechanism of toxicity, leading to the development of the same hazard trait. Restricting the definition to require similar toxicokinetic characteristics as part of "mechanistic similarity" would unnecessarily prevent important inferences for such chemicals from being drawn. The regulation does not preclude consideration of pharmacokinetics in evaluating whether or not one chemical may be mechanistically similar to another. It is DTSC's responsibility to prioritize chemicals based in part on hazard traits, and this aspect of the process is not covered by this regulation. Therefore, no changes were made to the regulation based on this comment.

16g. Comments on (g) "Other relevant data"

Some comments indicated that the definition of "other relevant data" was unclear, and did not allow for additional useful information to appear in the Clearinghouse, including volume of use, production, and potency. This is an example of such a comment.

> "These other relevant data are not restricted to only hazard traits, but could be any relevant data about a chemical in the TIC. Potential exposure is but one example." (GCA and ACI)

They commented further that use and application data (such as from the U.S.EPA's TSCA Inventory Update Rule) ought to be in the Clearinghouse under "other relevant data."

Response: The regulation was modified to add an additional section for inclusion of certain types of "other relevant data" in the Clearinghouse. The definition of "other relevant data" as it pertains to specific hazard traits was not changed. In discussing this change, OEHHA acknowledges that the additional section (Article 7) was not in the regulation at the time the comment was made.

The SB 509 statute mandates OEHHA to specify "any other relevant data" to be included in the Clearinghouse. This regulation provides for two different types of "any other relevant data" to be included: One specific type of "other relevant data" is provided in Articles 2-6 of the regulation, and another type in Article 7. The meaning of "other relevant data" in the definition is for *a specific hazard trait*:

> " 'Other relevant data' *for a specific hazard trait* means non-endpoint data, including chemical, physical, biochemical, biological or other data, that may indicate a chemical substance may have the hazard trait." [emphasis added]

This definition thus applies to Articles 2-6. Article 7 "Additional Relevant Data" was added to the regulation. This Article includes data that do not necessarily pertain to the issue of whether or not a chemical has a specific hazard trait.

Article 7 provides for the inclusion of important data on the inherent properties of chemicals – measures of exposure-response relationships such as potency and physiochemical properties. The term "any other relevant data" within the meaning of the statute includes other relevant data in Articles 2-6 as well as data specified in Article 7." Thus the regulation is primarily focused on hazard information, given that the purpose of

the Toxics Information Clearinghouse is to provide for the collection, maintenance, and distribution of information on specific chemical hazard traits.

There appears to be a concern that if other important, non-toxicological information is not being specified for inclusion in the Clearinghouse, it will not be considered in the DTSC consumer-products regulatory program. The information given as examples, such as use in commerce in the U.S. and specific applications, are examples of important data that DTSC can consider in fulfilling its mandates under AB 1879. Indeed, per Health and Safety Code section 25252, the prioritization process must include but not be limited to considerations of the volume of the chemical in commerce in the state and the potential for exposure in consumer products.

This regulation was developed in consultation with DTSC. The concept of other relevant data as used in the regulation, and the decision not to specify including information in on exposure and use, was explicitly discussed. DTSC agreed that other relevant data is primarily directed at the hazard traits and endpoints. DTSC also agreed that information on chemical use and applications belongs in their processes of identifying chemicals of concern and potential alternatives and eventual possible regulation. In fact, the statutory language of AB 1879 provides for DTSC to consider additional information beyond the specific types of information named. Opinions regarding the kinds of information that must be considered should be directed toward DTSC's regulatory process for implementing the AB 1879 statute.

In response to these and other comments OEHHA added Article 7 "Additional Relevant Data" and specifically included information on potency (exposure-response relationships) and on physicochemical properties.

16h. Comment on (h) "Toxicological endpoint"

GCA states:

> "[T]his definition lacks clarity because it is not specific to toxicity and the potential to cause harm. This definition should be revised as such, and additional definitions for other hazard trait endpoints should be defined as necessary." (GCA)

A similar statement was made by ACI.

Response: This definition is based on a standard, widely-accepted concept defining a toxicological endpoint as "a measured or otherwise observed adverse effect in a

biological system that indicates the presence of a hazard trait." As discussed in the ISOR, this definition is consistent with that used by US EPA. But to be explicit in incorporating the issue of harm, the term "adverse effect" was used in the regulation's definition. Adverse effect is also defined in the regulation to be a negative impact on the functioning of the organism. Thus, contrary to the comment, the definition does include the concept of potential to cause harm.

No change to the regulation was made based on this comment.

16i. Comment on (i) "Well-conducted scientific study"

- Point 1: GCA commented that the definition "might arbitrarily exclude any study which is not published in the open literature, or submitted to a government agency."

- Point 2: ACI suggested that the definition be revised to read

> "'Well-conducted scientific studies' means studies using methods and analyses which are scientifically valid according to internationally accepted principles."

- Point 3: PCPC and GCA commented that the term differed from DTSC's term "reliable information" in its previously proposed (and now withdrawn) regulation. PCPC also recommended that "OEHHA create a method for assessing the reliability, relevance and adequacy of underlying data before a chemical is added to the online Clearinghouse."

- Point 4: GCA recommended the term "well conducted scientific study" be deleted from the regulation and be replaced with the term "reliable information," defined as follows:

> "'Reliable information' is from studies or data generated according to valid accepted testing protocols in which the test parameters documented are based on specific testing guidelines or in which all parameters described are comparable to a guideline method. Where such studies or data are not available, the results from accepted models and quantitative structure activity relationship ("QSAR") approaches validated in keeping with OECD principles of validation for regulatory purposes may be considered. The methodology used by the Organization for Economic Cooperation and Development (OECD) in Chapter 3 of the Manual for Investigation of HPV

Chemicals (OECD Secretariat, July 2007) shall be used for the determination of reliable studies."

Response: With regard to the first point, it is not clear what important studies would be missed. Included are studies in the open literature as well as those conducted by or submitted to government agencies, "using methods and analyses which are scientifically valid according to generally accepted methods." As a point of clarification, "well conducted study" is defined in the regulation with regard to general advice on evidence of a hazard trait, and does not in any way indicate or specify data quality for inclusion of specific studies in the Clearinghouse.

With regard to the second point, the suggested definition is not much different than the regulation's definition of well-conducted study. This does not warrant a change in the regulation.

With regard to the third point, it is DTSC's responsibility under SB 509 to

"develop requirements and standards related to the design of the clearinghouse and data quality and test methods that govern the data that is eligible to be available through the clearinghouse." (Health and Safety Code 25256.2 (a)). OEHHA cannot address these points in its regulation as the comment suggests.

Defining the term "well-conducted study" in the regulation only pertains to general advice with respect to evaluating endpoint and other relevant data. The definition in no way sets a standard or a data quality requirement for the Clearinghouse. That is DTSC's mandate and responsibility.

With regard to the fourth point, this definition limits acceptable studies to those conducted within the limits of GLP guidelines or specific test methodologies published, for example, by OECD and used in testing the High Production Volume chemicals and pesticides. Guideline studies are essentially those that have followed prescribed quality control and reporting practices. As noted in the ISOR, so-called "guideline studies" are not synonymous with well-conducted studies. There is a vast and informative scientific literature, produced by academic institutions and through government research that would not be considered because it did not conform to such protocols. The World Health Organization's International Agency for Research on Cancer does not restrict itself to such studies in making decisions with regard to carcinogenicity, and utilizes much data in evaluating hazard that would be excluded under the proposed definition. Further, for many new and valuable methods of assessing chemical toxicity, there are no official guidelines from OECD or other institutions. Because the guideline methods such as OECD's are limited to specific tests, they do not include more recent scientific procedures or methodologies that have been accepted in the general scientific community, nor some important older procedures that are accepted in the scientific

research community. The scientific literature is full of well-conducted studies that are not "guideline" studies. To exclude these studies from consideration would not further the purposes of the Clearinghouse since it would exclude a wealth of relevant scientific information; this would likely be particularly problematic for alternatives analyses.

As noted above, DTSC is mandated under SB 509 to develop data quality requirements and standards that govern data eligibility for the Clearinghouse.

No change to the regulation was made based on these comments.

16j. Comment on (j) "Wildlife"

RMA commented that inclusion of

> "…all microorganisms in the definition of wildlife is extreme and may result in high costs to protect microorganisms that have little inherent societal benefit. The proposed rule defines wildlife to include all microorganisms. While there may be some microorganisms which warrant inclusion within the scope of the proposed rule, the use of all microorganisms is excessive. RMA recommends that the final regulation should be limited to microorganisms of significance to protection of human health and ecological communities."

Response: This regulation identifies the types of hazard trait, toxicological and environmental endpoint data that should be included in the Clearinghouse. Environmental endpoint data on microorganisms are important to understanding the potential effects of chemicals on communities or ecosystems. It is not practicable to define the limits of significant microorganisms in this regulation. The significance of the microorganism would be considered if the assignment of an environmental hazard trait relied on microorganism data. That would be case-specific and pursuant to AB 1879, such decisions will be made by DTSC.

No change to the regulation was made based on this comment.

Comments on Article 2 – Toxicological Hazard Traits – Carcinogenicity, Developmental Toxicity, and Reproductive Toxicity

17. General comments on Article 2

17a Comment: Language on bodies that recognize toxicity in 69402.2, 69402.4, and 69402.6

ACI expressed concern about “Recognition as a [hazard] by California, other states, the United States or other nations” as one of the criteria for strong evidence. They note this language does not take into account the competence of decision makers in other nations, and the lack of U.S. stakeholder input into decisions by other nations. They suggest we revise the section to make it clear it is only decisions by authoritative organizations, as defined in the regulation that should be recognized.

Response: The comment is correct that the language should refer back to “authoritative organizations” within the meaning of the regulation. The regulation was revised as follows to address the comment:

69402.2 (a) (7) Recognition as a known or potential carcinogen by ~~California, other states, the United States or other nations~~ an authoritative organization.

69404.4 (b) (3) Recognition as a suspected carcinogen~~, or the equivalent, by California, other states, the United States or other nations.~~ an authoritative organization.

69404.4 (a) (7) Recognition as a developmental toxicant by an authoritative organization ~~by California, other states, the United States or other nations~~.

69404.4 (b) (3) Recognition as a suspected developmental toxicant~~, or the equivalent, by California, other states, the United States or other nations.~~ an authoritative organization.

69404.6 (a) (6) ~~The chemical substance is recognized as a~~ Recognition as a ~~male or female~~ reproductive ~~hazard by California, other states, the United States or other nations~~ toxicant by an authoritative organization.

69404.6 (b) (2) Recognition as a suspected reproductive toxicant~~, or the equivalent, by California, other states, the United States or other nations.~~ an authoritative organization.

17b. Requirements of others to assess a hazard trait

One comment expressed concern that the regulation places certain requirements on others to carry out an assessment based on the criteria of an authoritative organization:

> "At numerous points in this Article, references are made to "meeting criteria" for various hazard classifications. OEHHA should make it clear that it is not requiring any organization to carry out its own assessment of hazards against criteria listed in the proposed regulation, but rather utilize available assessments of authoritative bodies with respect to the criteria." (ACI)

Response: The comment is correct that the regulation places no obligation on others to complete their own assessments. As noted in response to comments 4 and 5, the intent of these sections is to provide the user of the Clearinghouse some general guidance and information on what can be considered strong or suggestive evidence of a hazard trait. This regulation places no requirements on any organization. However, not including the guidance on strong versus suggestive evidence could lead users to wrongly conclude that all the evidence should be considered strong evidence that a given chemical has a particular hazard trait. No changes to the regulation were made based on this comment.

17c. Comment on different level of information between the ISOR and the regulation regarding weight-of-evidence for developmental and reproductive toxicity

While noting that "The supplemental information section [i.e., the ISOR] is principally sound", Dow notes

> *"…*overall, a significant loss of context occurred between the supplemental information and proposed regulation that inappropriately weights alternative methods of hazard identification (QSAR, cell-based assay, etc) equal to guideline studies designed to identify reproductive and developmental toxicants."

Response: The ISOR and the Final Statement of Reasons acknowledge that different types of information carry different weight when assigning hazard traits. This regulation does not provide an algorithm for the weighing of information or for making a definitive assignment of a hazard trait to a chemical. The assignment of hazard traits is the responsibility of DTSC under AB 1879. See responses to comment 5 above,

No changes to the regulation were made based o this comment.

18. **Comment on § 69402.3 Developmental Toxicity and § 69402.4 Evidence for Developmental Toxicity Hazard Trait**

Dow commented on developmental toxicity. Dow's main point regarding the developmental toxicity hazard trait in subsection 69402.3a is that

> "…the proposed regulation provides no allowances for exposure and is based simply on hazard."

Dow notes that information on toxicokinetics should be considered in defining developmental toxicity, citing as an example that ethylene glycol-induced rodent developmental toxicity resulting from "high bolus doses can result in non-relevant modes of action causing developmental toxicity due to altered toxicokinetics."

For the developmental toxicity endpoints in 69402.3b, Dow states that examples of developmental toxicity secondary to maternal toxicity have not been provided in the ISOR and that they should be to encourage weight of evidence approaches to developmental toxicity.

For the regulation's listing of other relevant data concerning developmental toxicity, Dow suggests a revision to 69402.3c – the addition indicated in underline below:

> "(c) Other relevant data <u>that may contribute to a weight of evidence evaluation for potential developmental toxicity</u> include, but are not limited to: mechanistic data at the … "

Dow also states that

> "There are currently no clearly established examples of "epigenetic toxicity". Reference to epigenetic toxicants seems out of place in this document and should be removed for the developmental toxicity hazard trait section."

OEHHA also received comments about weight of evidence and the SB 509 mandate for section 69402.4. These have been addressed under general comments above (see comments and responses 4 and 5 above).

Response: This regulation is hazard-based because SB 509 requires OEHHA to specify hazard traits, toxicological and environmental endpoints and other relevant data to be included in the Toxics Information Clearinghouse.

OEHHA agrees that maternal toxicity is an important consideration in evaluating developmental toxicity endpoint data. It is established that developmental toxicity can be secondary to maternal toxicity and indeed the US Environmental Protection Agency (US

EPA) has developed and utilizes guidance to evaluate evidence of developmental toxicity in light of maternal toxicity. The US EPA guidance is cited in the ISOR (pages 32 and 33), although as pointed out in the comments without specific reference to maternal toxicity. Other authoritative organizations such as the National Toxicology Program also utilize guidance and/or scientific judgment when evaluating developmental toxicity data in the presence of maternal toxicity. California considers maternal toxicity in listing chemicals with developmental endpoints under Proposition 65.[2] The Clearinghouse is a compilation of data on toxicological endpoints. Nothing in the regulation prohibits the inclusion in the Clearinghouse of "negative" or "null" studies that do not find effects or those studies for which results might be confounded by maternal toxicity or toxicokinetics. Although there can be clear cases, it is often difficult to entirely rule out developmental toxicity in the presence of maternal toxicity, as evidenced by US EPA Guidelines, or other confounders. Ultimately, however, the process for deciding whether or not a chemical has a hazard trait, or whether or not a particular study is included in the database is DTSC's (see response to comments 4 and 5 above).

As for epigenetic toxicants, there is a wealth of evidence that chemicals can alter epigenetic programming in utero, and there is also a large and growing volume of research and literature on linkages between such changes and diseases later in life.[3] Data on a chemical's impact on epigenetic programming subsequent to in utero chemical exposure should be compiled along with the other relevant data for the developmental toxicity endpoint in the Clearinghouse.

With regard to the suggested change to 69402.3c, the weighing of the evidence and decisions regarding hazard traits are DTSC's and are therefore not addressed in this regulation (see response to comments 4 and 5 above).

No changes were made to the regulation based on this comment.

19. Comments on § 69402.5 Reproductive Toxicity and § 69402.6 Evidence for Reproductive Toxicity Hazard Trait

Dow suggests the following rewording changes (in underline) in Section 69402.5:
(c) Other relevant data <u>that may contribute to a weight of evidence evaluation for potential reproductive toxicity</u> include but are not limited to: data on endocrine

[2] The Safe Drinking Water and Toxics Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 et seq.

[3] Gluckman PD, MA Hanson, CC Cooper, KL Thronburg N Engl J Med 359:61-73, 2008; Perera F, J Herbstman, Reprod Toxicol 31(3):363-373, 2011; International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100A: A Review of Human Carcinogens: Pharmaceuticals Diethylstilbestrol, page 177-220, 2011.

disruption, genotoxicity, in vitro measures of the capacity of a chemical to damage the function or structure of germ cells such as sperm or oocytes or cells critical for reproductive function, such as Sertoli and Leydig cells in males; structural or mechanistic similarity to other substances exhibiting the reproductive hazard trait."

Dow suggested the following wording changes, shown in underline and strikeout, in section 69402.6 on suggestive evidence for the reproductive toxicity hazard trait:

> "(b) Each of the following constitutes suggestive evidence and/or potential of reproductive toxicity for a given chemical substance:"
> "(1)…
> (3) ~~Strong~~ Based upon the supplemental information evidence for the Genotoxicity Hazard Trait per section 69403.5 or the Endocrine Toxicity Hazard Trait per section 69403.3 with mechanisms of genotoxicity or endocrine disruption likely to be involved in reproductive toxicity."
> (4) Strong supportive studies, as defined by the National Toxicology Program, indicating possible male or female reproductive toxicity.
> …

Dow and others make statements about weight of evidence and the SB 509 mandates for section 69402.6 that have been addressed under general comments above (see comments and responses 4 and 5 above).

Response: Regarding the suggested change for 69402.5, this section is specifying what data are to be included in the clearinghouse, and is giving a list of these data. This suggestion reflects concerns regarding how the data are to be used. These issues are discussed in response to comments 4 and 5 above.

Regarding the suggestions to change the wording in section 69402.6, the first change is unclear and would introduce new terminology to the regulation without adding clarity or purpose. It is not clear what "and/or potential of reproductive toxicity" means or what that would add to the existing term "suggestive evidence" in the regulation. The second suggestion is to add a reference to the ISOR (which they are terming supplemental information) in the regulation. While the ISOR along with this Final Statement of Reasons are part of the record for this regulation and can clarify its intent, it is unnecessary and inappropriate to cite the ISOR in the regulatory language itself. Deleting the word "strong" removes the consistency in the regulation and could cause confusion. With regard to the suggestion for (b)(4), the wording used is specific language in the National Toxicology Program's Explanation of Levels of Evidence for Reproductive Toxicity.

No changes were made to the regulation based on these comments.

Comments on Article 3 – Other Toxicological Hazard Traits

20. General Comment: the number of toxicological hazard traits

Some comments pertain to the number of toxicological hazard traits. The comment recommends a system that significantly reduces the number of toxicological hazard traits in the regulation by combining all the target organs together under "systemic toxicity" or "chronic toxicity" or "acute toxicity", which they suggest is better than the more detailed approach used in this regulation.

GCA writes:

> "OEHHA has justified its position on use of the long list of toxicities as hazard traits by stating that each trait was chosen in part because of listings within a textbook of toxicology, where discussions are broken out by target organ systems. Regardless of the fact that toxicology textbooks may organize information based on target organs, it is a generally accepted method for hazard identification to describe hazards in terms of either durations of exposure (*i.e.* toxic effects seen after acute exposure, toxic effects see after chronic exposures) or local versus systemic toxicity. Then, under the hazard trait of "systemic toxicity," the target organs would be identified (*i.e.* liver, kidney, heart, etc.).
>
> "It is also important to consider that none of the prominent national or international systems list the vast number of "icities" contained in the OEHHA proposal…Noting which organ system(s) is most sensitive is more than adequate to describe a chemical's hazard. Said differently, a single test can cover many different "icities," and the TIC should be structured in a way that makes that more apparent to users."

ACC expressed similar comments.

Response: The statement is incorrect in asserting that no prominent national or international agencies list hazards in a manner similar to this regulation and that a standard approach would be to list target organ toxicities under systemic toxicity. Here are some examples:

- NIOSH Pocket Guide: The US National Institute for Occupational Safety and Health, within the Centers for Disease Control and Prevention does not lump all toxicities into systemic toxicity. NIOSH was created at the same time as OSHA

with a mission to assure safe and healthy working conditions through information, research, education and training. NIOSH produces a pocket guide on chemicals in the workplace. For each chemical in the Pocket Guide, NIOSH provides lists of target organs and symptoms. So for example, for inorganic arsenic, the pocket guide lists target organs liver, kidney, skin, lungs, and lymphatic system; for benzene, the pocket guide lists eyes, skin, respiratory system, blood, central nervous system, bone marrow. The symptoms listed are akin to endpoints, which for arsenic are ulceration of the septum, dermatitis, gastrointestinal disturbances, peripheral neuropathy, respiratory irritation, and hyperpigmentation of the skin.

- OSHA. OSHA has proposed a rule to adapt the GHS for its Hazard Communication Standard (HCS). However, it has an existing HCS in place and in 2008 it released guidance[4] to assist the industry in meeting the standard. The current HCS guidance lists 17 types of chemical hazards that are "recommended for inclusion in the hazards profile for a chemical." The guidance given: "Reference source should be included for each item, where appropriate. In the event that no information on an item is known or it is not applicable, this should be indicated." It lists eight specific target organ effects, and contrary to the statement in the GCA comment, it does not include these under systemic effects. Systemic effects include carcinogenicity along with other general health effects. After noting that "virtually any organ or organ system may potentially be at risk," it indicates that "data in the literature search pertaining to other organs must also be evaluated and documented." It included in "other important health effects" the cardiovascular system and immune system because they are "most likely to be reported for industrial chemicals." Thus under the 2008 guidance for complying with the HCS, a number of target organ hazards are listed. The table below provides the hazards explicitly named in the guidance for inclusion in the HCS.

OSHA (2008) Hazard Communication Standard (HCS) Guidance SUMMARY of Known or Suspected Health Effects

Systemic Effects	Target Organ Effects	Other Important Health Effects
▪ Carcinogen ▪ Toxic	▪ Hepatotoxicity ▪ Nephrotoxicity	▪ Cardiovascular toxicity

[4] Occupational Safety and Health Administration, 2008, Guidance for Hazard Determination for Compliance with the OSHA Hazard Communication Standard (29 CFR 1910.1200),

▪ Highly Toxic ▪ Irritant ▪ Corrosive ▪ Sensitizer	▪ Neurotoxicity ▪ Blood/hematopoietic toxicity ▪ Respiratory toxicity ▪ Reproductive effects (includes genetic toxicity) ▪ Cutaneous hazard ▪ Eye hazard	▪ Immune toxicity ▪ Others

- When evaluating hazards of chemicals to support decision-making for environmental programs (e.g., drinking water, air emissions), both the US Environmental Protection Agency (US EPA) and Cal/EPA discuss in detail in their health-effects documents the types of hazards associated with exposure to a chemical. They do not combine them into single categories of “acute” or “chronic” toxicity or “local” or “systemic toxicity”. The assessments are tailored to the hazards posed by the chemical. For example, US EPA’s Integrated Science Assessment for Ozone has sections on respiratory effects, cardiovascular effects, reproductive and developmental effects, central nervous system effects, and carcinogenic and genotoxic potential, and mortality. US EPA’s recently released trichloroethylene document has chapters on genetic toxicity, central nervous system toxicity, kidney toxicity and cancer, liver toxicity and cancer, immunotoxicity and cancers of the immune system, reproductive and developmental toxicity, and other site specific cancers, and a hazard characterizations for neuro-, kidney, liver, immuno-, respiratory, reproductive and developmental toxicity and cancer. It does not have a hazard characterization entitled “systemic toxicity.”

While the comments suggest that the overall categories of acute toxicity, chronic toxicity, or systemic toxicity would suffice for hazard identification, the examples show that other well-respected authorities have decided otherwise. The Toxics Information Clearinghouse is meant to be a compilation of the available information on the toxicity of a chemical to facilitate the evaluation of chemicals in consumer products and alternatives. The general hazard traits, along with the endpoint data, including positive and negative studies on toxicity to the various organ systems will give the user full appreciation of what is known about the chemical and its possible substitute.

Further, noting which organ system is the most sensitive is part of dose-response assessment and risk assessment, not hazard identification. It is insufficient to understand the toxicity of a chemical if one only notes the most sensitive organ system, and would exclude information that should be available in the Clearinghouse.

No change to the regulation was made based on this comment.

21. General Comment: Adaptive versus adverse effects

One comment called for the regulation to clearly distinguish adaptive responses from adverse effects:

> "An adverse effect is not any known biochemical or chemical change, or even any known or measureable precursor along a biochemical pathway that could lead to some degree of perturbation. Consideration of adversity occurs when perturbations are sufficiently large, which may depend upon susceptibility of the host. ACC believes that many of the listed effects on pages 10-16 for individual hazard traits are not adverse effects but adaptive effects…By including discussion of effects that can be adaptive only within the OEHHA proposal for certain hazard traits, OEHHA fails to distinguish between these critical concepts of toxicology. If OEHHA includes the current level of detail within endpoint lists for each hazard trait, the proposal needs to be modified to clearly define the difference between an adaptive response and an adverse effect." (ACC)

Response: The regulation lists toxicological endpoints that meet the definition in the regulation:

> A "toxicological endpoint" for a specific hazard trait is a measured or otherwise observed adverse effect in a biological system that indicates the presence of the hazard trait.

Thus toxicological endpoints are observed adverse effects, defined in regulation as follows:

> "Adverse effect" for toxicological hazard traits and endpoints means a biochemical change, functional impairment, or pathologic lesion that negatively affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge."

The issue of whether a response is adverse or adaptive can be the subject of debate when evaluating chemicals. Sometimes an adaptive response is simply that, and there

are no long term impacts on the organism. This type of response would not be considered an adverse effect under this regulation. Other times, the organism can adapt but its functional reserve is depleted leaving the organism more vulnerable to future impacts. This would be considered an adverse effect in this regulation, and observations of it in a study would be toxicological endpoints. Sometimes the inability to adapt occurs in a segment of the population. For example, sometimes a chemical may elicit a very mild adaptive response in a one individual, and in another individual may exacerbate asthma.

Some effects may appear adaptive but may represent "other relevant data" for a specific hazard trait within the meaning of the regulation; that is, they *may indicate* a chemical substance may have the hazard trait. The ACC comments, "A change in glucose or glycogen metabolism without some accompanying change in tissue histopathology or organ function would not be considered an adverse effect." Under the regulation, disruption of glycose or glycogen metabolism is therefore not considered a toxicological endpoint, but is considered "other relevant data" for the hepatotoxicity and gastrointestinal toxicity hazard trait. Effects that are adaptive, but that may indicate a chemical has a toxicological hazard trait, are treated as "other relevant data" under this regulation and are specified for inclusion in the clearinghouse.

Deciding whether a particular chemical has a hazard trait is the responsibility of DTSC as laid out in AB 1879. This regulation describes the types of information that should be available in a Toxics Information Clearinghouse, and gives non-exclusive examples of toxicological endpoints and other relevant data. It does not prescribe how this information must be used by DTSC or anyone else. No change to the regulation was made based on this comment.

22. Comments: on suggesting additional hazard traits - Neurodevelopmental

Comments were received recommending the inclusion of a neurodevelopmental hazard trait:

> "Testing for neurodevelopmental effects is not commonly done, leading to inadequate management of these effects and tremendous costs. The current draft proposal will exacerbate this problem because it treats data about reproductive and development effects as being identical to data about neurodevelopmental effects. This is simply not the case. In many or all of the national and international testing regimes, a distinction is made between testing protocols that are capable of detecting reproductive effects, developmental effects, and neurodevelopmental effects. The testing protocols that are deemed

acceptable in regimes such as REACH for detecting developmental effects are not designed to and would not detect neurodevelopmental effects if they occurred. Consequently, a chemical can be tested and found to be "negative" for developmental effects without obtaining any information whatsoever about whether it might cause neurodevelopmental effects. …I would recommend that this be explicitly addressed in the design of the clearinghouse so that it is easy to determine whether information is available for a chemical about this issue and whether there is any cause for concern." (Kyle)

"… include neuro-developmental effects and the impacts of low level exposures" to "further strengthen" the draft rules" (CWA)

Response: OEHHA agrees that many chemicals are not specifically tested for developmental neurotoxicity and that this adverse health effect is very important. Not all developmental toxicity testing comprehensively evaluates neurotoxicity in the developing organism. But it is also true that not every developmental toxicity test covers all organs and may miss many things.

Neurodevelopmental toxicity is a type of neurotoxicity and also a type of developmental toxicity. Given the importance of developmental neurotoxicity for infants and children, this has been added as a separate hazard trait in response to these comments

As regards including "impacts from low-level exposures," the meaning of the comment was not entirely clear. The regulation specifies toxicological and environmental endpoints and other relevant data. It does not provide a process for conducting an impact exposure-response assessment, although in Article 7 measures of exposure-response relationships such as potency are specified and may assist users in this evaluation.

23. Comment on including cumulative impacts

One comment suggested the regulation "include cumulative impacts to encourage further study". (CWA)

Response: As required by SB 509, the regulation specifies hazard traits, endpoints and any other relevant data that should be included in the Clearinghouse. Assessing cumulative impacts involves analyzing and synthesizing information about many stressors, including chemical hazards, typically in a specific geographic region or specific subpopulation. The hazard trait, endpoint and other data in the Clearinghouse might be relevant for such an assessment. However, such an assessment would clearly

be beyond the scope of this regulation. The Clearinghouse is a repository of information, not a risk assessment or cumulative impacts assessment tool. No change to the regulation was made based on this comment.

24. Comment on section 69403.3: Endocrine Toxicity as hazard trait

Some comments stated that endocrine toxicity should not be included in the regulation as a hazard trait:

> "The listing of endocrine toxicity as a unique hazard trait is somewhat redundant when reproductive and developmental toxicity are listed."(GCA)
>
> "For emerging traits, such as endocrine disruption, the Council strongly believes that it is inappropriate to include them in the proposed regulation as "other" toxicological hazard traits." (GMA)
>
> "With regard to "emerging" traits, endocrine disruption (Section 69403.3) and epigenetics (Section 69403.4), for example, are mechanisms of potential toxicity, not toxic end-points themselves and thus not hazard traits. As such, OEHHA should not unilaterally establish these or other new hazard traits" (GCA, page 13).
>
> "ACC believes that it is inappropriate to include the emerging concepts of endocrine disruption and epigenetics as "other" toxicological hazard traits.

Response: The hazard trait in section 69403.3 is "endocrine toxicity," not endocrine disruption, and is defined in the regulation as "the occurrence of adverse effects following exposure to a chemical substance on the structure or function of the endocrine system, including endocrine disruption and metabolic syndrome" (Section 69403.3a).

Endocrine toxicity is not a newly recognized chemical hazard. US EPA under its IRIS program currently has established 15 reference doses (RfDs) and reference concentrations (RfCs) on thyroid toxicity endpoints, and several others based on other forms of endocrine toxicity (e.g., adrenal and pituitary endpoints). Two of these were based on endocrine disruption: The RfC for hydrogen cyanide and cyanide salts is based on thyroid enlargement and altered iodide uptake, and the perchlorate RfD is also based on iodide uptake inhibition. Regarding the latter example, the National Academy of Sciences National Research Council 2005 Report, "Health Implications of Perchlorate Ingestion," concluded that the RfD for perchlorate should be set on an endocrine disruption endpoint.

While endocrine toxicity has important relationships to reproductive and developmental toxicity, it can be manifested as other adverse health effects, as evidenced in some of the US EPA assessments noted above. For example, interference with the thyroid can lead to metabolic disturbances unrelated to reproduction and development that are involved in human morbidity and mortality. Endocrine toxicity is defined as a hazard trait in this regulation, recognizing that endocrine toxicity can be manifested as other toxicities. As noted above, the term “hazard trait” is not in common use – no other organization is using this term.

No change to the regulation was made based on the comments.

25. Comments on Section 69403.3: Endocrine Toxicity Endpoints and Data

25a. Comment on endocrine disruption as a mode of action: ACC and GCA made similar comments that endocrine disruption was not an endpoint but a mode of action, and that the standard practice is to describe toxic effects in such instances by apical endpoints of the adverse effect. They further state that modulation of the endocrine processes may or may not give rise to adverse effects.

> **Response:** The toxicological endpoints related to endocrine disruption in the regulation include the adverse perturbations of fundamental biological processes - the synthesis, secretion, transport, binding, action, or elimination of natural hormones or their receptors in the body that are responsible for the maintenance of homeostasis, metabolism, reproduction, development or behavior (see response to comment 21 above). These processes when adversely disrupted result in a number of human diseases, including cancer, birth defects, infertility, bone loss, and thus are relevant for a number of toxicological hazard traits. The endpoints covered here are those perturbations that can lead to adverse effects.

The endpoints related to endocrine disruption are based on the US EPA definition for endocrine disruption Effects of interest that may or may not represent adverse outcomes would be included as other relevant data.

> The hazard traits and toxicological endpoints are not linear, but rather relational (see ISOR Section 69404.1). Because of the complexity of an organism, a chemical can produce effects in more than one organ and often the direct impact on one system leads to an impact on another to which it is physiologically tied.
>
> Genotoxicity has long been recognized as a property of chemicals that should be avoided and much product development in the pesticide and chemical industry has sought to avoid this endpoint. Genotoxicity is a mode of action for carcinogenicity,

reproductive toxicity and developmental toxicity, and the non-apical endpoints of genotoxicity are used in characterizing chemicals. This has been standard practice for the past 30 years. The focus on endocrine disruption is more recent.

Mechanistic hazard traits and endpoints, which are often related to early steps in disease processes, are expected over time to be of increasing importance in toxicology evaluations. The field of toxicology is moving away from large-scale animal testing and toward these more upstream endpoints. The regulation provides for the inclusion of such data in the Clearinghouse, as other relevant data, or endpoints depending on the understanding regarding the endpoint and the degree that it is an indicator of adverse health.

No changes were made to the regulation based on this comment.

25b. Comment on requiring validated testing protocols: GCA stated that "many of the endpoints listed in this section have not been validated as unique endpoints for identifying endocrine toxicity of chemicals," and PCPC similarly stated that there should be scientific consensus on "trait characterization and validated testing protocols *before* including them in the proposed regulation and online clearinghouse."

Response: The issues raised regarding data quality and validation fall outside OEHHA's mandate under SB 509 to specify hazard traits, endpoints and other relevant data for the clearinghouse. Under SB 509, DTSC is responsible for establishing data-quality standards and requirements for the Clearinghouse. Similarly, DTSC is responsible under AB 1879 for weighing and evaluating data on hazards from the Clearinghouse and other types of information in evaluating chemicals and alternatives.

No changes were made to the regulation based on this comment.

25c. Comment on including metabolic syndrome within endocrine toxicity: Dow noted that "OEHHA should be complimented on including the word "adverse" in their definition of endocrine toxicity as this is omitted in most regulatory endocrine communications," but then questioned the inclusion of metabolic syndrome under endocrine toxicity, noting that "the commonly accepted causes of metabolic syndrome are genetics, insulin resistance, obesity, lifestyle, and age."

Response: The comment names commonly accepted risk factors for metabolic syndrome. It is also noted that recent studies have demonstrated that endocrine disruptors can increase obesity, and thyroid hormone dysfunction is also associated with insulin resistance. There is also growing evidence that certain endocrine disruptors

can change programming to favor an increase of adipocytes. Studies also show a relationship between thyroid hormone dysfunction and metabolic syndrome. Endpoint and "other relevant data" on studies showing the potential for a chemical to cause metabolic syndrome are specified for inclusion in the Clearinghouse.

No changes were made to the regulation based on this comment.

25d. Comment on limiting endocrine toxicity to androgen, estrogen and thyroid endpoints: Dow states that the definition of endocrine toxicity in the regulation is "too ubiquitous". They give as an example that high dose overt toxicity could lead to disruption of homeostasis and metabolism. Dow recommends "that OEHHA employ the US EPA strategy of using EAT endpoints to evaluate endocrine toxicity."

Response: U.S. EPA has focused on developing tests to detect chemicals that disrupt estrogen (the E in EAT), androgen (the A in EAT), and thyroid (the T in EAT) hormone systems in its endocrine disruptors screening program. The U.S. EPA does not say that these EAT endpoints are the only type of endocrine toxicity possible, and indeed has established guidance values for use in its risk evaluations based on non-EAT endocrine endpoints (e.g., Reference Doses (RfDs) or Concentrations (RfCs) for chlorodifluoromethane, Savey and cumene).

Restricting the focus of endocrine toxicity endpoints to only EAT endpoints would not capture the full suite of endocrine toxicities, and would exclude important endocrine toxicity endpoints. These include (but are not limited to) endpoints related to major control functions of the hypothalamic-pituitary axis, the metabolic control systems involving pancreatic and adrenal hormones, and calcium and phosphate homeostasis (important for bone physiology, proper function of nerves and muscles) regulated by the parathyroid hormones. Thus, these regulations include non-EAT endpoints under endocrine toxicity.

With regard to endpoints related to changes in homeostasis, these are included to the extent that they result from adverse perturbations of natural hormones, not overt toxicity, in accordance with the regulation:

> "Endocrine toxicity endpoints include but are not limited to those indicating: adverse effects on endocrine organs; adverse perturbations of the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body which are responsible for the maintenance of homeostasis, reproduction, development and or behavior."

No changes to the regulation were made based on these comments.

25e. Comment on weight of evidence for endocrine disruption: Referring to the ISOR section on other relevant data for the endocrine toxicity hazard trait, Dow also noted that

> "This is a straight forward approach but lacks a weight of evidence evaluation. Unfortunately, EPA has yet to create a weight of evidence approach for endocrine disruption. The OEHHA document does not address whether a weak estrogen receptor binding assay result would result in a compound being evaluated as endocrine toxic."

Response: The response to comment 5 explains that this regulation identifies information for inclusion in the Clearinghouse, and that it is DTSC's mandate under AB 1879 to weigh the evidence and make evaluations using data in the Clearinghouse.

No changes were made to the regulation based on this comment.

26. Comments on Section 69403.3 - epigenetic toxicity

Some comments objected to the inclusion of epigenetic toxicity as a hazard trait.

26a. Epigenetic toxicity as a hazard trait. As with endocrine toxicity, GCA and ACC commented that epigenetic toxicity should not be included as a hazard trait. (see comment 24 above)

> "Epigenetic toxicity is an even newer concept within toxicology and has been examined as the basis for identifying mechanisms of systemic toxicity. In fact, "epigenetics" is defined as a mechanism of action for potential toxic effects, not an endpoint for toxicity testing." (GCA)
>
> "OEHHA fails to provide any scientific basis for including "epigenetic toxicity" as a separate discrete hazard trait from systemic toxicity." (ACC)

Response: OEHHA agrees that epigenetic toxicity is a relatively new field and that test methods are still developing. Nonetheless, OEHHA does not agree that it is premature to include epigenetic toxicity as a hazard trait. To the extent that information is available, it should be included in the Clearinghouse.

Epigenetic toxicity can result in any number of adverse outcomes due to cellular dysregulation following sufficiently altered gene expression, which are discussed in detail in the ISOR. While this is a mechanism of toxicity for other general organ toxicities, it is also being treated as a type of toxicity in and of itself, similar to

genotoxicity. As explained in the ISOR, hazard traits are relational – some hazard traits may be endpoints for other hazard traits.

There is a wealth of evidence that chemicals can alter epigenetic programming in utero, and there is also a large volume of research and growing literature on linkages between such changes and diseases later in life.[5] Data on a chemical's impact on epigenetic programming subsequent to in utero chemical exposure should be compiled along with the other relevant data for the developmental toxicity endpoint in the Clearinghouse. DTSC has the mandate to consider data quality and decide which data are appropriate for inclusion in the Clearinghouse, and, per SB 509 to assign hazard traits to chemicals.

No changes were made to the regulation based on this comment.

26b. Adverse or adaptive epigenetic responses. GCA states that the definition in the regulation is "overly broad as it could include adaptive as well as adverse effects on organism." ACI called for clarifying "what constitutes an adverse outcome with respect to epigenetic toxicity". Similarly Dow notes:

> "The definition of epigenetic toxicity needs to emphasize that epigenetic changes are a part of normal cellular function and development… The current definition is too broad and needs revision because it does not distinguish toxicant-induced from normal epigenetic alterations; hence any change in the epigenome would be considered "toxicity"…The bottom line is that normal variability and interaction between different epigenetic modifications needs to be fully understood before test results could be understood." (Dow)

Response: In the regulation, the epigenetic toxicity hazard trait is defined as changes, at the cellular or organism level, in gene expression or gene function that do not involve changes in the DNA sequence, following exposure to a chemical substance. We agree that this was not specific enough to distinguish adverse effects from adaptation to an environmental cue. Based on these comments OEHHA amended (underline) the definition to read:

> "The epigenetic toxicity hazard trait is defined as changes, at the cellular or organism level, in gene expression or gene function that do not involve changes

[5] Gluckman PD, MA Hanson, CC Cooper, KL Thronburg N Engl J Med 359:61-73; Perera F, J Herbstman, Reprod Toxicol 31(3):363-373; International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100A: A Review of Human Carcinogens: Pharmaceuticals Diethylstilbestrol, page 177-220, 2011.

in the DNA sequence, and contribute to adverse effects in an organism following exposure to a chemical substance."

26c. Epigenetic data and testing

"Current publications indicate that the state-of-the-science for epigenetic toxicity testing is not sufficient to support epigenetic screening… Absolutely necessary is the need to establish a direct causative relationship of chemically-induced epigenetic changes (adaptive or adverse) and adverse health outcome, which is obviously not possible without understanding normal variability. …. At this time Epigenetic Toxicity should be removed as a Hazard Trait and information from these assays should be considered as other relevant information." (Dow)

Response: This regulation does not specify testing requirements. The inclusion of epigenetic toxicity as a hazard trait specifies the inclusion in the Clearinghouse of data on the relationships between chemical exposure and epigenetic outcome. Pursuant to SB 509, DTSC has the mandate for data quality requirements for the Clearinghouse. That is outside the scope of this regulation.

No changes were made to the regulation based on this comment.

26d. Comment on removing a statement from the regulatory text: Dow comments that the statement "… identification of genes that are subject to DNA methylation…" is not appropriate and should be deleted from the regulatory text. They further note that all genes are presumably subject to and require epigenetic modification.

Response: The words highlighted for deletion are not in the text of the regulation. It is a phrase at the end of a sentence in the ISOR. That paragraph reads:

"There are a number of laboratory methods that are currently used to evaluate the status and patterns of DNA methylation in cells or tissues. In general, these methods include a combination of methylation detection strategies and identification of genes that are subject to DNA methylation."

The latter part of the second sentence is what the comment is referencing. The commenter's point is fair as the phrase is not clear. One complexity in associating epigenetic changes in genes with subsequent disease is figuring out what specific genes, and loci within the gene, are most important in terms of epigenetic modification that results in disease. Thus, the phrase would have more clearly been written as, "…identification of the most important genes involved in disease subject to DNA methylation."

No change to the regulation was made based on this comment.

27. Comment on Section 69403.8 – Immunotoxicity

Comments on the immunotoxicity endpoints in the regulation were that they are a mix of outcomes, syndromes, and measurable effects:

> "…there is no context in their relative significance…[T]here has to be tiered approach in terms of what experimental data you would need in order to be able to determine whether sufficient or insufficient to conclude upon immunotoxicity." (GCA)

As regards other relevant data the question was asked:

> "… is there some other more specific text that provides the context for what evidence is needed to substantiate structural/mechanistic similarity?" (GCA)

Response: The toxicological endpoints listed in subsection 69403.8 (b) are some of the adverse outcomes already being measured in studies assessing the immunotoxicity of chemicals. Immunotoxicity assays include both in vivo (whole animal) and a repertoire of in vitro and ex vivo assays which are well-developed and in common use. As the regulation and ISOR note, the list does not include all possible toxicological endpoints for immunotoxicity as there are too many to name, and the science continues to evolve.

This regulation specifies the hazard traits, endpoints and other relevant data to be included in the Clearinghouse. The regulation does not provide a process to determine what chemicals have a specific hazard trait. As discussed in responses to comment 4 above, relative significance is not relevant to this regulation because it pertains to weighing of the evidence, and this regulation does not assign hazard traits. More discussion of this point is given in response to comments 4 and 5 above.

The response to comment 16f above provides more context for the meaning of mechanistic similarity, as the term is used in the regulation.

No change to the regulation was made based on the comments.

28. Comment on Section 69403.12 – Ocular Toxicity

Comment: "Ocular toxicity is an endpoint commonly addressed through testing for eye irritation and damage in standard acute toxicity tests in animals. As a result, ocular effects are included as a hazard trait within many classification systems. Since testing for eye irritation, for example, is commonly included within standard toxicity testing batteries, it is unclear why OEHHA has chosen to deviate from the standard approach to identifying hazards to the eye." (GCA)

Response: There are many possible adverse effects on the eye other than irritation. In this regulation, OEHHA is identifying endpoints that may not be picked up by standard test regimes for eye irritation but that nevertheless adversely affect the eye. These are intended to be inclusive of the full range of ocular toxicity endpoints, including eye irritation, that may be observed in studies. Many of the toxicological endpoints for ocular toxicity in the regulation are commonly used endpoints in tests (see references to standard toxicological textbooks in the ISOR (pp 82-84).

No change to the regulation was made based on this comment.

Comment: "OEHHA may want to consider adding "color perception," which is sometimes affected by chemical solvent exposures, to its 69403.12(b) list of endpoints." (CDPH)

Response: We agree that color perception is an endpoint of ocular toxicity, and is measured in epidemiological studies of workers exposed to solvents. However, the list of endpoints is nonexclusive. Thus, observation of this endpoint could indicate that a chemical poses an ocular toxicity hazard.

No change to the regulation was made based on this comment.

29. Comments on Section 69403.14 – Reactivity in Biological System

"[R]eactivity in biological systems is an overly broad trait that is not useful for hazard evaluation since all chemicals could be considered to "react" with biological systems simply by being absorbed into a cell. The endpoints mentioned in the OEHHA proposal appear to fit more easily within other hazard trait categories as underlying mechanisms or modes of action." (GCA)

"…reactivity in biological systems plays a role in mitigating hazard/toxicity, and thus is not always an "adverse" hazard trait. For example, Phase II conjugations

> which result in rapid elimination; or reactivity of substance with water (hydrolysis) such as with isocyanates, can result in diminished or eliminated hazard properties of a parent substance." (Dow)

Comments received also indicated that this section should "specify what constitutes an adverse outcome with respect to reactivity in biological systems" (GCA, ACI).

PCRM writes:

> "It is unclear why *in vitro* indicators of reactivity in biological systems would be considered only "other relevant" data; detoxification and metabolism attributes of substances can be discovered and/or confirmed using other lines of evidence."

Response: The definition of the Reactivity in Biological Systems hazard trait clearly states that the trait is addressing negative health outcomes:

> "The reactivity in biological systems hazard trait is defined as the occurrence of rapid reactions with molecules in the body that lead to alterations in critical molecular function and ultimately ***adverse health*** outcomes." (Section 69403.14(a), emphasis added)

As noted in the ISOR (pages 86-87) and the definition, reactive chemicals react rapidly and can cause critical and adverse alterations in cellular function at the molecular level, leading to adverse health outcomes. Reactive chemicals can produce adverse outcomes in any organ or tissue to which they are distributed. Reactive chemicals can be detoxified by reaction with conjugating chemicals (Phase II metabolic reactions) in the body, or can react with water and hydrolyze, and these processes determine the magnitude of effect. The toxicological endpoints are directed at in vivo measurements of effects of reactive chemicals, and this in part addresses the issue of degree of detoxification noted in the comments. Because of the inherently hazardous nature of biologically reactive chemicals, information on them is important for inclusion in the Clearinghouse.

In response to the comment regarding in vitro data, in vitro data can provide evidence for the reactivity in biological systems hazard trait, and that is why they are included as other relevant data. It is difficult to draw a bright line for some hazard traits between what might be considered an endpoint and what might be considered other relevant data. This is one of those cases. In the end, the regulation emphasized *in vivo* evidence in examples of endpoints in order to account for rapid detoxification, which might not be obvious in some *in vitro* systems. Note, however, that DTSC can consider

in vitro evidence as well as *in vivo* evidence in deciding whether a chemical has the reactivity in biological systems hazard trait.

No change to the regulation was made based on these comments.

30. Comments on Section 69403.15 – Respiratory Toxicity

30a. Comment: GCA commented that although respiratory toxicity is a standard endpoint measured in acute and chronic toxicity studies, they did not see the reason to specify respiratory toxicity separate from the generic "systemic toxicity." Concern was expressed that "some of the endpoints listed in the proposal have not been validated as indicators of adverse effects as opposed to adaptive changes (*e.g.* increased inflammatory cytokine expression.)" (GCA) Dow expressed similar concern regarding distinguishing between adverse functional endpoints and biochemical measures which may or may not represent an adverse effect.

GCA and CalNIN suggested the addition of language in the regulation addressing insignificant versus significant exposures to chemicals causing respiratory toxicity. GCA recommends the addition of language at the end of 69403.15 (c), to clarify intent to deal with significant exposure threats. GCA stated, "In interpreting the above, anticipated exposure must be detectable or significant at levels above background."

CalNIN made a similar comment.

Dow states that "the inherent toxicity of the inhaled particle/fiber needs to be included in any definition of hazard – including the impact of dissolution and physical clearance on pulmonary retention and species differences in clearance rates and routes." (Dow)

GCA and CalNIN also note "… the inclusion in this definition of "particle size distribution inclusive of respirable particles; respirable fibers;" This is appropriately applied as a consideration relevant specifically to Respiratory Toxicity." (GCA, CalNIN)

Dow writes: "The impact of particle size distribution on the site of deposition was discussed but the size classification discussed in section 69405.7 refers to particles ≤10 microns (PM_{10}) while current ambient particle regulations are based on particles ≤2.5 microns. Absent is any discussion of the fraction of particles (or gases) that are deposited and absorbed – or inhaled dose in general. The regulatory text should be expanded to discussion of the above point."

Response: We agree with the comment regarding the importance of respiratory toxicity; it is a commonly studied toxicity from chemical exposures. Systemic toxicity is an overarching and vague description of the capability of a chemical to induce adverse responses in an organism away from the site of application, and does not provide any detail on which organs are affected. Thus, the regulation includes more specific hazard traits than the generic "systemic toxicity".

As for the concern that cytokine expression may be adaptive and not adverse, cytokine expression in the lung is used in animal studies as an indication of the inflammatory properties of chemicals on the lung. What might be considered an adaptive response to some is seen as an adverse response to others. This is something that would be considered when DTSC identifies and prioritizes chemicals under AB 1879. This regulation does not evaluate specific chemicals, assign hazard traits, or assess risk. As required by SB 509, this regulation identifies hazard traits, toxicological and environmental endpoints, and any other relevant data to be included in the Clearinghouse.

The issue of significant exposure and potency (inherent toxicity) of chemicals are important topics for assessing risk, and are appropriately dealt with under the process DTSC will use for identification and prioritization of chemicals of concern under AB 1879. The regulation for SB 509 does not classify chemicals, assign hazard traits or estimate risk. Thus exposure and potency, while important to determining hazard, are not "hazard traits" as the term is defined in regulation. However, given the importance of potency of a chemical to assessing overall risk of exposure, based on these and other comments, OEHHA added Article 7 "Additional Relevant Data" to the regulation. This includes potency (exposure-response relationship, Subsection 69407.1) as part of the information to be included in the Clearinghouse.

In response to the comment on particle size, the particle size cut point of ≤10 microns is commonly used to delineate particles small enough to be inhaled into the respiratory tract. There are regulatory standards for PM10 in California (the Ambient Air Quality Standards set by the Air Resources Board). The fraction deposited and where in the respiratory tree deposition occurs depends on the distribution of particle size, the morphometry of the respiratory tract and a number of other complex factors. More specific discussion of this issue can be found in the documents cited in the ISOR (e.g., page 88).

No change to the regulation was made based on this comment.

30b. Comment: Respiratory hazard trait and particles

The RMA states:

> "... The proposed rule also greatly reduces the evidence needed to classify a particle or fiber as possessing a respiratory toxicity hazard trait," and
>
> "The criteria proposed to determine whether particles or fibers possess a hazard trait would be dramatically narrowed,.."

RMA cites the discussion of the suggestive evidence in the regulation for "other toxicological hazard traits" and then interprets its meaning for whether or not a particle or fiber would have the respiratory toxicity hazard. In doing so, RMA considers the discussion of the respiratory hazard trait in the ISOR. RMA speculates about what conclusions will be reached regarding carcinogenicity.

The comment goes on at length about the relevance of rat "lung overburdening studies" to humans for determining whether a particle is carcinogenic. The commenter states

> "Epidemiological data with humans exposed to very high levels of fine particulates (e.g., studies of exposure to high levels of carbon black, coal, talc, diesel exhaust, silica, among others) demonstrate that lung overburdening does not occur in humans and there are no increased rates of lung cancer in such workers."

The comment also states "the extreme criteria cited in the proposed rule for classifying particles and fibers as carcinogenic is inconsistent (with) a number or recommendations of findings of expert panel(s)", and states that different scientific bodies and individual scientists have concluded that the rat lung overburdening studies are not relevant to cancer in humans.

Response: This regulation does not provide specific criteria to assign a toxicological hazard trait to a specific kind of particle or fiber. The regulation specifies the hazard traits, toxicological and environmental endpoints and other relevant data that should be included in the Toxics Information Clearinghouse, as mandated by SB 509. It does not prescribe either a process or criteria for determining that a substance has a hazard trait. This is discussed at greater length in responses to comments 4 and 5 above.

The comment that there is no elevated risk to workers exposed to crystalline silica or diesel engine exhaust is incorrect. Crystalline silica is a widely recognized human lung

carcinogen. For example, it is identified as a known human carcinogen by IARC. Diesel engine exhaust is associated with elevated risk of lung cancer in workers and is identified as a Toxic Air Contaminant in California. This regulation is not a risk assessment regulation, and does not describe processes, procedures, or data requirements for risk assessment. No change to the regulation was made based on these comments as they are not relevant to this regulation.

30c. **Comment**: CDPH expresses concern that particles larger than 10 µm in diameter - up to 100 µm are potentially inhalable and can cause respiratory toxicity in the upper airways. The comment suggests the term "inhalable" rather than "respirable" be used in the list of other relevant data for the respiratory toxicity hazard trait. CDPH notes potential for confusion between the occupational literature and the hazard trait regulation:

> "69403.15(c) lists "particle size distributions inclusive of respirable particles" and "respirable fibers" as relevant data for respiratory toxicity. OEHHA may be using the term "respirable" in this context to mean "capable of being breathed." However, use of this term in industrial hygiene is associated with a specific size range of particles capable of reaching the alveolar region of the respiratory system (e.g., defined by NIOSH as a size distribution with a 50% cut point of aerodynamic equivalent diameter of 4.0 µm). Particles that are larger than those included in the "respirable size" may deposit in the tracheobronchial or head-airways regions of the respiratory system and exert their toxic effects at those locations (e.g., acid mists), or migrate elsewhere in the body such as by being swallowed and then entering the bloodstream (e.g., lead particles). OEHHA should use the term "inhalable" or "inspirable" rather than "respirable" in this section of the proposed regulation. "Inhalable" particles are usually considered (in the fields of industrial hygiene and aerosol science) to range in aerodynamic size up to 100 microns. It should be made clear that particle sizes up to 100 microns are inhalable and should be considered for respiratory toxicity."

Response: There is a difference in how the term respirable is used between the occupational literature and the environmental toxicology literature and regulatory discussions of ambient airborne particulate matter. There has been a focus in the environmental literature on particles that can reach the deep lung. That is why ambient air regulations have focused on PM 10, or particulate matter with a mass median aerodynamic diameter of 10 µm or less. That is the view of the term "respirable" taken in this section of the regulation. On the other hand, the comment is correct in saying that particles larger than 10 µm are inhalable, that is can be breathed in, and can be associated with toxicity as they may affect the nose, mouth and upper airways or be

deposited and swallowed. Those types of toxicity affecting the upper airways would be endpoints of respiratory toxicity and covered under the respiratory toxicity hazard trait. The definition of the respiratory hazard trait includes the entire respiratory tract, from the upper respiratory tract, airways and lung. Evidence of toxicity to the nasal or oral epithelium or upper airways is covered in the endpoints of respiratory toxicity and could be considered when evaluating chemicals for this hazard trait. Concerns regarding swallowing larger particles with subsequent uptake through the gut would be addressed by other types of toxicological hazard traits depending on the organ or system affected. Finally, even though particle sizes greater than 100 µm are not called out as other relevant data, the list provided is non-exclusive.

No changes were made to the regulation based on this comment.

32. Comments on respiratory toxicity description in the Initial Statement of Reasons

32a. Comment: Dow commented on the following statement in the ISOR: "The ubiquitous nature of air pollutants impacting the lung has large measurable adverse public health impacts." Dow asserted that the number of ambient air pollutants with measureable public health impacts is fewer than suggested by the text. They principally cited ozone, SO_2, NO_2 and ambient particulate matter. They requested a modification of the sentence to make that clear.

Response: We agree that the number of air pollutants with known large measurable impacts is limited to the ubiquitous air pollutants that have been studied the most -- ozone, particulate matter, NO_2 and the other criteria air pollutants. However, the statement is still true – the pollutants regulated in California as "criteria air pollutants" are ubiquitous and have large measurable adverse public health impacts. No changes were made to the regulation based on this comment.

32b. Comment: Regarding the statement in the ISOR, "In all cases, the extent of damage is dependent on the chemical concentration to which animals or people are exposed." Dow said::

> "This is a simplistic and misleading statement. The text correctly points out that for particulate phase chemicals, the site of deposition is dependent on the particle size distribution and, for gases, water solubility greatly impacts the site of exposure. What is missing is any link to the key exposure metric - deposited or absorbed dose, or differences in inherent toxicity of different inhaled materials, or the impact of the presence or absence of sensitive cell populations or (species –

specific) metabolic enzyme systems. These elements need to be expanded on in the regulatory text." (Dow)

Response: The ISOR description is much less detailed than a toxicology textbook. The references cited provide much more detail and are part of the public record for the regulation. Both the potency of a chemical to induce an adverse response and exposure to the chemical are important to assessing risk.

OEHHA added Article 7, "Additional Relevant Data" to the regulation that specifically includes exposure-response information.

32c. Comment: NAIMA also commented on the ISOR explanation of respiratory toxicity:

"Respiratory tract toxicity is a very common endpoint and can be influenced by numerous factors identified in a broad array of assays and other data. The examples of "other relevant data" should be expanded beyond "water soluble," to include, for example, "'biosoluble" (solubility in biologic fluids). Similarly, the "long half-life in the lung" example should be expanded to include broader hazard assays, concepts, and endpoints, such as those measuring biopersistence. The value of modestly expanding the examples can be seen in the biopersistence assays used by the European Union ("EU") to evaluate potential fiber toxicity." (NAIMA)

Response: The ISOR was provided to explain the reasoning behind the proposed regulation. OEHHA acknowledges that there are a number of examples that could have been included in the ISOR under other relevant data and the other toxicological endpoints. No changes were made in the regulation based on this comment.

33. Comments on respiratory toxicity description in Initial Statement of Reasons – specific toxicological endpoints

33a. Comment:

"It should be noted that measurement of sensory irritation in animals or 'irritation' in human studies are all responses that occur prior to injury. They may be good data to help set occupational exposure levels but they should not be equated to chemical toxicity." (Dow)

Response: OEHHA disagrees that irritation is not chemical toxicity. Both sensory irritation and irritation resulting from tissue damage are the basis of a number of regulatory values (Reference Exposure Levels) in California. While one could argue that sensory irritation is simply the response of stimulated trigeminal nerves, most people would consider such irritation adverse. Irritation can result from actual tissue damage. Many chemicals can be both sensory irritants via trigeminal nerve stimulation and induce tissue damage at similar or higher exposures. No change to the regulation was made based on this comment.

33b. Comment: Pathologic evaluation of the respiratory system is "an essential element of understanding toxicity of inhaled materials under controlled laboratory conditions…[but] the regulatory text should acknowledge and address shortcomings of the data for assessing human health hazards". (Dow)

Response: The ISOR is not as detailed as a textbook of toxicology. The regulation identifies the hazard traits and types of information to be included in the Clearinghouse. It does not set out a process or criteria for using that information to assign hazard traits to chemicals or conducting human health assessments. No change to the regulation was made in response to this comment.

33c. Comment: Regarding the composition of bronchoalveolar lavage fluid (BALF):

> "This is another powerful experimental tool to investigate acute and chronic responses under controlled conditions with understanding of exposure history. For humans, this may provide key information on the inflammatory status of the conducting airways and gas exchange region, but should not be used as a diagnostic aide… Exhaled breath analysis is actually a better endpoint for humans – assessing inflammatory/oxidative stress status of the individual. But it is non-specific except in the case of known exposure (but exposure concentration and duration are generally missing)." (Dow)

Response: The composition of bronchoalveolar lavage fluid (BALF) is an important tool for assessing the adverse health impacts of chemicals. The composition of BALF is used as a "diagnostic aide" in both humans and animals, and is an important tool in assessing the impact of chemicals on the respiratory and immune system. In humans, BALF composition has been used in controlled exposure studies occasionally, but is somewhat invasive. Hence lung function assays are more common in human controlled exposure studies and in the clinical setting. Exhaled breath analysis is also used in evaluating inflammatory responses in the lung, as the comment notes. No change to the regulation was made based on this comment.

34. Comments on respiratory toxicity description in Initial Statement of Reasons – other relevant data

34a. Comment: Regarding endpoints measured in isolated or cultured cells:

> "[T]he relevance of these data are dependent on detailed characterization of test material in the test system, the dosimetry to the cells, and the relevance of the exposure route (submerged vs air/liquid interface) and cell type. Exposures using explants can help cross species comparisons and may be more relevant because the 3D structure and cell-cell interactions are retained. The text needs to be modified to reflect the relevance and reliability for using these types of data in the assessment of a hazard trait. Just because "endpoints" are measureable does not mean that they are indicative of an adverse outcome." (Dow)

Response: The ISOR provides very brief descriptions of some types of studies that are done to evaluate respiratory system toxicity. The purpose of the ISOR is to provide the intent of the regulation. It is not possible for the SOR to be a detailed treatise on the various areas of toxicology. The regulation and accompanying ISOR do not describe criteria on data quality or data relevance from any specific type of in vitro toxicity test method. The regulation does not assign hazards traits, assess risk or classify chemicals. As required by SB 509, it identifies hazard traits, toxicological and environmental endpoints, and any other relevant data to be included in the Clearinghouse, a repository of information on toxicity and potential toxicity of chemicals in commerce. The responsibility for data quality and reliability is given to DTSC under SB 509 and AB 1879 as they identify and prioritize chemicals of concern and assess alternatives. No changes were made to the regulation based on this comment.

34b. Comment: Regarding discussion of other relevant data for respiratory toxicity, a comment on the need to consider exposure and the inherent toxicity of an inhaled particle or fiber was made: "Recognition of the inherent toxicity of the inhaled particle/fiber needs to be included in any definition of hazard…" (Dow)

Response: As noted in comments above, exposure is a consideration that is appropriate for prioritizing chemicals and products. It is not an inherent hazard trait of a chemical. This regulation is not about risk assessment.

As far as potency is concerned OEHHA added Article 7 and included exposure-response information as other relevant data for the Clearinghouse as we recognize the importance of such information in prioritizing chemicals.

No changes to the regulation were made based on these comments.

35. Comments on Section 69403.16 – Evidence for Toxicological Hazard Traits

Several comments expressed concern that the regulation would require DTSC to determine that a chemical has a hazard trait based on suggestive evidence. Some comments stated that including descriptions of categories of information indicating strong or suggestive evidence for toxicological hazard traits is an overstep of authority. Others discussed weighing of evidence, and the need to consider positive and negative studies. Another comment is concerned that there is an evaluation of the evidence by doing a study count.

> "Yet, while Section 69403.16 Evidence for Toxicological Hazard Traits proposes a framework for evaluating scientific results, it is not a WOE [weight-of-evidence] approach. Instead, OEHHA is proposing to simply count the positive studies. OEHHA's approach fails to consider all the relevant information required for a causal determination and falls well short of the scientific standard of practice for weight of evidence evaluation in toxicity determinations." (GCA)

Response: The same or similar comments arose in the discussion of the other sections on suggestive and strong evidence. These comments are responded to in response to comment 4 above.

With respect to this particular section, OEHHA agrees that the available information has to be viewed in the overall context of the total database on a chemical in deciding whether or not a chemical has a hazard trait. Thus, in response to this comment and others with a similar concern, Section 69403.17(a)(2) was reworded to indicate that, for strong evidence, "the available data from well-conducted scientific studies show that exposure to the chemical substance induces a toxicological endpoint…" Similarly Section 69403.17(b)(2) was reworded to indicate that, for suggestive evidence, " the available evidence from well conducted scientific studies suggests exposure to the chemical substance induces a toxicological endpoint…" No changes to the regulation were made based on these comments.

36. Comment: Article 3 & 4 – Endpoint lists

> "Each of the toxicological and environmental traits in the OEHHA proposal is accompanied by a list of possible endpoints that could demonstrate that a chemical has the respective trait. However, the hazard traits and endpoints listed are not actual hazard traits or endpoints. Rather, much of what is listed in the draft are preludes in multiple-step pathways that may or may not lead to disease or an adverse outcome (i.e., these are actually mechanisms and not endpoints; examples include epigenetic adverse perturbations and electrophilic potential). This will not further the Green Chemistry goals or provide the certainty necessary to make prioritization decisions or weigh chemical alternatives." (GCA p 15)

Response:

OEHHA disagrees with this comment. With regard to the statement that toxicological hazard traits and endpoints in the regulation are not actual hazard traits or endpoints, the Initial Statement of Reasons explains that the hazard traits cover the major toxicities of concern in the field of toxicology. Further many of the specific toxicological endpoints in the regulation are from standard toxicity studies. Other endpoints that may be reported in epidemiological or clinical studies are also covered. Finally the endpoint specifications also provide for the inclusion of findings from state of the art research being conducted in government, industry and academic research laboratories. Standard toxicological guidelines used by US EPA and other bodies have been used as the basis of defining endpoints when they exist. Standard toxicological texts were also utilized.

As noted in the Initial Statement of Reasons, the hazard traits and endpoints are relational, not linear. For example, the hazard trait genotoxicity is also a toxicological endpoint measured in assessing the potential carcinogenicity and developmental toxicity of a substance. The reactivity in biological systems hazard trait captures inherent physicochemical properties of chemicals and is an indicator of a chemical's ability to cause toxicity in a biological system. The reasons for these and other hazard traits are explained more fully in the relevant sections of the Initial Statement of Reasons.

No change to the regulation was made based on this comment.

37. General comments on Article 4 – Environmental Hazard Traits

Five submissions were received directly commenting on Article 4: the GCA, ACI, Dow, RMA and PCRM. Several stakeholders expressed support for the GCA's comments including ACC, Amway, CalNIN, DuPont, GMA, Koch, NPA, P&G and PCPC. These

groups also signed the GCA submission. In addition, Koch expressed support for the comments on the Environmental Hazard Traits made by ACI.

37a. Comment: Some comments stated that OEHHA should limit the environmental hazard traits to inherent chemical properties. For example,

> "OEHHA has identified several complex processes that are influenced by numerous biological, chemical and physical factors within the ecosystem (e.g., eutrophication, loss of biological diversity) and attempted to characterize them as being the result of an individual inherent property of a chemical. While these processes are important concerns regarding the health of an ecosystem they cannot be readily attributed to a particular chemical alone. The environmental hazard traits should focus on toxicity to wildlife including plants and animals." (ACI)

Response: OEHHA disagrees that complex processes cannot be linked to individual chemicals. Chemicals can drive processes that adversely change ecosystems or ecosystem components. A chemical need not be the sole cause of the hazardous ecological outcome in order to pose a hazard. Environmental conditions that interact with contaminant effects to form complex ecological impacts are commonly present in natural systems. For example, eutrophication is prevalent in the environment because higher water temperatures and low water column mixing commonly occur in watersheds that receive excess nutrients. The fact that nutrients will not lead to eutrophication in all receiving waters is not justification to ignore the environmental hazard posed by excess nutrients in ecosystems. Additionally, single species toxicity tests do not consider indirect effects of contaminants on species interactions and thus are insufficient in assessing adverse impacts of chemicals on communities and ecosystems. These issues are further addressed in OEHHA's responses to specific comments on individual environmental hazard traits below. No change to the regulation was made based on this comment.

37b. Comment: It was also asserted that field data should not be used in the hazard trait. For instance:

> "[P]otential effects in the field exist in the context of multiple stressors and it is frequently not possible to parse out the causative stressor(s) responsible for the observed effect. Use of field data will require additional confirmatory data, e.g., from lab studies, etc., in order to be indicative of a particular hazard trait in most instances. This includes data on things like wildlife reproductive impairment based on field data." (GCA)

Response: The regulation establishes the types of data that should be included in the Clearinghouse. It does not set out criteria for using information to assign a hazard trait to a chemical. That falls under the DTSC mandates in AB 1879. Field data can be valuable when evaluating the evidence for environmental toxicity of a chemical. Exclusion of all field data would be inconsistent with OEHHA's mandate under SB 509 to identify relevant data to be included in the Toxics Information Clearinghouse. This regulation does not require anyone to assign a hazard trait based on field data; it identifies those data that should be available in the Clearinghouse. No change to the regulation was made based on this comment.

37c. Comment: A U.S. EPA QSAR model is available to predict binding of pesticide inerts to the fish estrogen receptor. Similarly, the in vitro fish embryo toxicity assay "has been in use for several years by Germany to test effluent toxicity levels." (PCRM)

Response: Comment noted. The regulation does not establish or describe all specific testing methods, and cannot of necessity include all the test methods in existence. Information from all scientifically valid methods would be appropriate to include in the Clearinghouse. No changes were made to the regulation based on this comment.

37d. Comment:

> "Ecological effects should not include any effect on an individual organism. The proposed rule inappropriately equates adverse health effects on humans and ecological effects. However, the ecological risk assessment work is much less well-developed than the risk assessment framework for human health risks. The breadth of the change is further highlighted by DTSC's expansion of ecological adverse effects from population affects to include any effect on any individual organism. Given the genetic diversity in any species, this expands adverse effects to any biological effect in any individual organism." (RMA)

Response: The regulation does not equate human health risks with ecological risks. The environmental hazard traits focus on protection of populations, communities and ecosystems. Ecotoxicologists use data on test groups of individuals to predict effects at higher levels of biological organization. This approach is consistent with the U.S. Environmental Protection Agency's Guidelines for Ecological Risk Assessment, cited in the Initial Statement of Reasons. No change to the regulation was made based on this comment.

38. Comments on Section 69404.1 – Domesticated Animal Toxicity

Several comments questioned OEHHA's inclusion of a separate hazard trait to address domesticated animals. Domesticated animals were said to be covered adequately under the wildlife hazard traits. DOW, GCA and ACI viewed the purpose of using a separate hazard trait for domesticated animals an attempt to address exposure, which is not consistent with the overall goal of the regulations.

> "While the value of livestock and pets is not argued, the value of these animals should not be confused or co-mingled with intrinsic hazard. The example of melamine in cat and dog food is given as an example; however, would not the ingestion of melamine by any mammal (regardless of domestication) result in adverse effects? Consider revising the regulatory text to appropriately focus on the intrinsic hazard and avoid confusing this point with the societal factors." (Dow)

> "This section is unnecessary in that it is making a distinction with respect to the inherent toxicity of a chemical based on the route of exposure of that chemical, which is not an inherent property. … This section should be eliminated and any data which might be included in the TIC that is relevant to domesticated species should be generally included with all other data for animals and wildlife." (GCA, ACI)

Response: Domesticated animal toxicity was included as a separate hazard trait for several reasons. The terms "domesticated" and "wild" are contradictory; therefore including domesticated animals under the wildlife definition would have been an error. Additionally, there are differences between these groups of animals that may affect the determination of a hazard from a chemical. Most importantly, domesticated animals are valued on an individual basis, whereas wildlife is generally protected at the population-level (organism-level data are used to predict population-level impacts). This difference becomes relevant when evaluating the mode of action and potency of chemicals. For example, a chemical found to cause a low-severity rash in mouse studies might be assigned the human health Dermatotoxicity hazard trait and the Domesticated Animal Toxicity hazard trait, but not the Wildlife Survival Impairment hazard trait. In addition, physiological differences between wildlife and domesticated animals do exist. A history of selective breeding leads to decreased genetic diversity in domesticated animals. Animal husbandry and pet ownership decrease the generalized stress related to survival in the wild. These differences could influence the toxicological response, but are less likely to affect hazard trait findings. No change to the regulation was made based on this comment.

39. Comments on Section 69404.2 – Eutrophication

Two comments stated that this hazard trait should be eliminated. For example:

> "This proposed hazard trait section is unnecessary, lacks clarity and should therefore be eliminated. Eutrophication is a complex process that is influenced by a number of physical, biological and chemical factors within the ecosystem. It is not an inherent property of a chemical, and therefore, should not be considered a hazard trait of a chemical." (GCA; ACI provided similar comments)

Response: Eutrophication is among the top threats to California's lakes and rivers. Anthropogenic nutrient loading is a strong driver of eutrophication. Commercial products represent one component of anthropogenic nutrient loading. Other drivers of eutrophication, such as warmer temperatures and stagnant waters, are common in California, as evidenced by the high incidence of eutrophication in the State.

Commercial products have been linked to cultural (anthropogenic) eutrophication. Extensive eutrophication in the Great Lakes was addressed through the control of phosphates in detergents and improved wastewater treatment. In some areas of California, wastewater treatment removes a portion of excess nutrients, but many treatment plants remove little to no nutrients from wastewaters. Additionally, most of California's storm water is not treated for excess nutrients. Currently several counties and states are limiting the levels of phosphorus allowed in detergents and lawn fertilizers. No change to the regulation was made based on these comments.

40. Comments on Section 69404.3 – Impairment of Waste Management Organisms

> "This proposed hazard trait is unnecessary and should therefore be eliminated." (GCA)

> "While there are specific internationally-accepted, standardized tests to determine the potential for a chemical to impact organism in biological waste treatment systems, it is just another facet of environmental toxicity. The regulations would be clearer if generally accepted terminology was used rather than California developing new terminology." (GCA, ACI)

Response: OEHHA disagrees that impairment of waste management organisms in wastewater treatment facilities and septic systems is just another facet of environmental toxicity. Waste management organisms operate in a mostly closed system and are

manipulated to achieve the most efficient performance. Mortality in these systems leads to very different consequences than mortality in natural microbial communities. Loss of microorganism cultures in waste treatment processes results in the buildup of hazardous (pathogenic) waste. Reestablishing effective microbial treatment requires much time and expense. Septic systems often include warnings that certain products can kill treatment organisms. Additionally, wastewater treatment districts attempt to educate the public on the dangers involved in disposing of some products down the drain. By identifying this hazard trait, OEHHA is addressing an important and longstanding issue that was brought up in comments from wastewater treatment groups during the informal pre-regulatory comment period. No change to the regulation was made based on this comment.

41. Comments on Section 69404.4 – Loss of Genetic Diversity, Including Biodiversity

41a. Comment:

> **"**This proposed hazard trait is unnecessary and should be removed. The potential for a chemical to adversely affect the community structure of an ecosystem is no different than the environmental toxicity of a chemical. Moreover, it is not possible to objectively quantify the effect a chemical may have on a particular ecosystem since the health of any ecosystem will be the subject of a great number of factors." (GCA)

Response: OEHHA disagrees that the potential for a chemical to adversely affect the community structure of an ecosystem is no different than the environmental toxicity of a chemical. While biodiversity is affected through direct effects like those of DDT on bird reproduction, chemicals also affect interactions between species like predator-prey interaction and competition for resources. Impacts on species interactions can alter community structure and effect biodiversity. In addition, changes in biodiversity result from a cascade of indirect effects where the impact on one species dramatically affects community structure. For example, decreased ability of a top predator to control an herbivore prey species can lead to increased abundance of the herbivore and depletion of the primary producers consumed by the herbivores. Such trophic cascades can deplete the base of food webs (e.g., phytoplankton) or remove important habitat (e.g., kelp beds) in ecological communities. In this example, the top predator may maintain a viable population by switching prey sources. Single species toxicity tests do not consider effects of contaminants on species interactions as well as indirect effects, and thus are insufficient in assessing adverse impacts of chemicals on communities and ecosystems. No change to the regulation was made based on this comment.

41b. Comment: Dow commented that genotoxicity to terrestrial wildlife needs a sufficient historical control to place data into assay context and perspective. This should be included in the regulation.

Response: The regulation does not identify specific testing methods. The Initial Statement of Reasons explains that methods used in the studies contributing data to the clearinghouse must be scientifically valid and must be conducted according to generally accepted principles. The study of genotoxicity in wildlife is well established and is supported by decades of genetic study in the field of ecology. This comment suggests a data-quality requirement that falls under DTSC's regulatory purview and is outside the scope of this regulation. No change to the regulation was made based on this comment.

42. Comments on Section 69404.5 – Phytotoxicity

> "Since this is the first time that in vitro evidence is discussed in the context of environmental hazard trait, it may be important to highlight the fact that *in vitro* approaches are not always predictive of whole organism effects for any number of reasons (*e.g.* whole organism physiology and metabolism capabilities are not always reflected in *in vitro* data). It would be useful to suggest that the text be altered throughout the document to indicate that *in vitro* data can only be used to indicate the hazard trait when it can be conclusively demonstrated that the *in vitro* effect is directly related to an apical, whole-organism effect of interest." (GCA)

Response: As required by SB 509, this regulation establishes the types of data that should be included in the Clearinghouse. It does not set out criteria for how one uses the information to assign a hazard trait to a chemical. That falls under the DTSC mandates in SB 509 and AB 1879. We agree that it is appropriate to use *in vitro* data when evaluating the evidence for toxicity of a chemical. That is why we include this type of information in the other relevant data and sometimes in the toxicological endpoints when they are validated and routinely used. This regulation does not require anyone to assign a hazard trait based on mechanistic data; it simply says those data should be available in the Clearinghouse. No change to the regulation was made based on this comment.

43. Comments on Section 69404.10 – Evidence for Environmental Hazard Traits

Some commenters thought this section was an overstep of authority:

> "This entire section is unnecessary and unauthorized by the statute (SB 509) in that the office is attempting to classify chemicals when it is only authorized to specify hazard traits and endpoints. Furthermore, while it will be critical that only high quality information is included in the Toxics Information Clearinghouse (TIC), it is the purview of the Department of Toxic Substances Control to establish the criteria for inclusion of any particular study, or other data or information in the TIC." (GCA, ACI)

Another comment stated a concern that listing of a chemical by an authoritative organization such as chemicals on U.S. EPA's water contaminants list should not be equated to posing a hazard:

> "It should be considered that the occurrence of a substance on a contaminant list does not constitute a hazard. For example, toluene diisocyanate is included on U.S. EPA's CCL3 list of drinking water contaminants, yet this substance cannot exist as dissolved in water. Clearly, the authorities which make these designations or lists are not always well-informed of the technical relevance or reality of including substances on such regulatory lists. OHEEA must spell out provisions for critically evaluating information and decisions derived from such lists, thereby avoiding the propagation of errors made by other "authorities"." (Dow)

Response: This regulation does not classify any chemical as having hazard traits or determine whether a chemical poses a hazard. This section of the regulation provides general guidance that can help DTSC, product manufacturers, non-governmental organizations and other Clearinghouse users better understand the information relating to a given chemical and its possible environmental hazard traits. The rationale for defining strong and suggestive evidence for environmental hazard traits and an explanation of this section's compliance with SB 509 are the same as those discussed in the response to Comment 4 regarding strong and suggestive evidence for toxicological hazard traits.

DTSC has the authority to set data-quality requirements and standards for the Clearinghouse, and to assign hazard traits to specific chemicals. In doing so, DTSC could choose to take into account arguments such as Dow's contention that toluene diisocyanate does not belong on a federal water contaminant list. However, the

possibility that an authoritative organization's actions on a single chemical can be questioned does not negate the value of viewing that organization's findings on the impacts of chemicals as evidence of a hazard trait.

No change to the regulation was made based on this comment.

44. General comments on Article 5 – Exposure Potential Hazard Traits

44a. Comment: Inclusion of Article 5

Several comments disagreed with the inclusion of exposure potential hazard traits in the regulation:

> "The "exposure potential hazard trait" concept should be stricken from this regulation. Exposure potential is not a hazard. Rather hazard is an intrinsic trait that requires adequate exposure to demonstrate the hazard, i.e., hazards can only be manifest when the exposures are sufficiently high." (GCA)

The same or similar comments were submitted by CalNIN, SOCMA, and ACC.

GCA and ACC indicated that consideration of exposure potential should be included instead in a category of "other relevant data". For example:

> "Some individual items within this section (*e.g.* bioaccumulation, environmental persistence) are important chemical properties that are often reported and for which there may be substantial data to populate the TIC. While it is fair to consider these properties as "other relevant data" and include them in the TIC as such, they should not be considered stand-alone hazard traits."(GCA)

Another concern was that a chemical could be prioritized as of concern based only on its exposure potential hazard traits, and that the toxicity of the material, not just exposure needs to be considered:

> "While exposure potential is certainly germane to risk, it is so only in the context of a particular chemical having a specific hazard associated with it….We therefore recommend deletion of this section and incorporation of relevant parameters of exposure potential directly into each of the descriptions of the toxicological hazard traits. If such information is to be incorporated into the Clearinghouse and the larger regulatory framework, it should be expressly stated that these considerations are not relevant in isolation and should not be the basis for any categorization or classification for purposes of these regulations

> independent of any specific information relating to a toxicological hazard." (CalNIN)

Response: OEHHA disagrees that exposure potential should not be a class of hazard traits. These are inherent properties of chemicals that affect the degree of exposure to chemical substances, or in the case of global warming potential exposure to adverse environmental conditions including heat, experienced by humans and wildlife. Because they are intrinsic properties of chemicals that increase the potential for health or environmental risk, they are hazard traits, and not simply "other relevant data." Many of the hazard traits that fall into this section are also considered important components of chemical regulation by a number of other state, national and international government agencies charged with environmental protection including bioaccumulation, persistence, ambient ozone formation, global warming potential, and stratospheric ozone depletion, as discussed in the Initial Statement of Reasons.

The information in the Clearinghouse on exposure potential will be important to the prioritization of chemicals by DTSC as well as to assessment of potential alternatives. Comments regarding how these traits should be incorporated into the larger regulatory framework are relevant to DTSC in its development of processes to AB 1879.

No change to the regulation was made based on these comments.

44b. Comment: One comment states that several sections in Article 5 are subject to existing regulations:

> "Additionally, the following sections in Article 5 are currently subject to existing regulations set forth by the U.S. EPA's National Ambient Air Quality Standards, U.S. EPA's Stratospheric Protection Division's Regulations, and/or California Air Resources Board's (CARB's) Greenhouse Gas Rules.
>
> - o Section 69405.1 Ambient Ozone Formation;
> - o Section 69405.4 Global Warming Potential;
> - o Section 69405.7 Particle Size or Fiber Dimension; and
> - o Section 69405.8 Stratospheric Ozone Depletion Potential.
>
> "SB 509 states: "The department shall not duplicate or adopt conflicting regulations for product categories already regulated or subject to pending regulation consistent with the purposes of this article." Therefore, if Article 5 is

not deleted, an exemption from each of the sections referenced above should be included for products subject to current and draft regulations." (GCA)

Response: DTSC will determine how it will use chemical-specific information relating to these four hazard traits. Regulation of products is beyond the scope of this regulation, and therefore the suggestion to include regulatory exemptions in this regulation is inconsistent with its purpose. No change to the regulation was made based on this comment.

44c. Comments on Section 69405.1 – Ambient Ozone Formation

"Ozone formation is not a hazard trait and should therefore be removed from the regulation. By definition of the reference cited in OEHHA's draft regulation, "Ozone, the tri-atomic form of oxygen, is a gaseous atmospheric constituent. In the troposphere, ozone is created both naturally and by photochemical reactions involving gases resulting from human activities." The formation of ozone may result in measurable concentrations that reach an effect level for organisms that are exposed; however ozone formation in itself is not a hazard trait." (GCA)

Response: OEHHA disagrees. The ability to form tropospheric ozone is an inherent property of a chemical substance that results in increased exposure to health risks, and therefore can be appropriately identified as a hazard trait. For this reason it has been a concern to state, national and international regulatory agencies. Arguably the most important achievement of modern environmental-regulatory programs in California and the United States has been the dramatic reduction in ambient ozone levels as a result of the reduction in emissions of chemicals that contribute to ozone formation. No change to the regulation was made based on this comment.

44d. Comments on Section 69405.2 – Bioaccumulation

Some comments objected to bioaccumulation as a hazard trait:

"… [B]ioaccumulation is not a hazard trait and should be removed from the regulation as such. Although bioaccumulation has been defined by various credible entities, none have defined it as a hazard trait. That said, it is an important inherent chemical property that is often measured and reported. As such, it could be included in the Toxics Information Clearinghouse as "other relevant data."" (GCA)

> "… [B]ioaccumulation is not a hazard trait, however it is an important inherent chemical property that is often measured and reported. As such, it should be included in the Toxics Information Clearinghouse as "other relevant data." (ACI)

One comment objected to subsection 69405.2(b):

> "… OEHHA has proposed to classify chemicals as a bioaccumulation hazard if its bioaccumulation factor (BAF) is greater than 1000, or it has a log octanol-water partition coefficient greater than or equal to 5. Bioaccumulation is not a hazard, and OEHHA has neither the mandate nor the authority to be classifying chemicals as such. Therefore, this classification aspect of bioaccumulation should be eliminated." (GCA)

Suggestions for appropriate bioaccumulation data to be included in the Clearinghouse were made:

> "OEHHA should use the best available science when identifying appropriate bioaccumulation data to be included in the TIC. Recently, the Society of Environmental Toxicology and Chemistry (SETAC) conducted a Pellston workshop on POPs and PBTs that explored the current state of bioaccumulation science. Much of this science was discussed at the May 2010 OEHHA workshop in Berkeley, California on *Indicators of Ecotoxicity Hazards and Exposure Potential*. The SETAC workshop developed the following definition for a bioaccumulative substance: "A substance is considered bioaccumulative if it biomagnifies in food chains." Standard criteria for reporting the extent to which a chemical may bioaccumulate were noted including bioconcentration factor (BCF), bioaccumulation factor (BAF), biomagnification factor (BMF, both laboratory and field), trophic magnification factor (TMF), octanol-water partition coefficient (KOW) and octanol-air partition coefficient (KOA). The workgroup concluded that the most relevant bioaccumulation criterion is the trophic magnification factor (TMF; also referred to as a "food-web magnification factor"); in the absence of data on the TMF, the BMF (either derived in the laboratory or based on field data) is a reliable indicator. They also concluded that "BCF is no longer recognized to be a good descriptor of the biomagnifications capacity of chemical substances." One criterion found in the OEHHA proposed regulation that was not the subject of the SETAC exercise is "inhibition of an efflux transporter;" this concept is not generally accepted by the scientific community as a measure of the potential for a compound to bioaccumulate and should be eliminated from the OEHHA proposal. OEHHA should consider including the other six criteria (BCF,

BAF, BMF, TMF, KOW, and KOA) in the TIC as "other relevant data" as they are common chemical measures." (GCA).

Response: Numerous regulatory agencies in the U.S. and internationally view bioaccumulation as an important aspect of chemical fate, as discussed in the Initial Statement of Reasons. The potential to bioaccumulate is an inherent property of a chemical that results in increased exposure to the chemical and potential for health risks in wildlife or humans, and therefore can be appropriately identified as a hazard trait. Thus, OEHHA disagrees that bioaccumulation is not a hazard trait.

OEHHA evaluated the SETAC workshop[6] noted in the comment by GCA and amended the text of the bioaccumulation hazard trait to include additional measures indicative of bioaccumulative potential, based on the information cited. For purposes of this regulation, bioaccumulation includes the uptake and retention of a chemical in an organism and does not necessarily imply that concentrations of the chemical in the exposed organism are greater than those in the exposure media (e.g., food, water, air, soil). Bioaccumulation is the net result of absorption, distribution, metabolism, and elimination of a chemical substance in an organism, and thus involves complex processes. The amended text includes additional various means of measuring bioaccumulation in addition to BAF.

44e. Comment: A comment recommended that the following text be added to the sections on bioaccumulation:

> "Unlike organic substances, the bioaccumulation potential of metals cannot be estimated using octanol–water partition coefficients (Kow) or bioconcentration and bioaccumulation factors (BCFs and BAFs). For metals, BCFs and BAFs are inversely related to exposure concentration and are not reliable predictors of chronic toxicity, food chain accumulation, or hazard. The U.S. EPA's Framework for Metals Risk Assessment provides specific guidance on how to assess bioaccumulation potential for metals and metal substances." (NAMC)

Response: There is text in the regulation indicating that data demonstrating bioaccumulation is information to consider when evaluating the evidence for a chemical's ability to bioaccumulate. This is applicable to both organic compounds and metals. As pointed out in the comment, chemical properties such as Kow, BCF and BAF are somewhat problematic for assessing bioaccumulation of metals. Some models

[6] Gobas FAPC, DeWolf W, Burkhard LP, Verbruggen E, Plotzke K. Revisiting bioaccumulation criteria for POPs and PBT assessments. Integrated Environmental Assessment and Management 5:624-637.

have been developed to evaluate bioaccumulation of metal compounds and would be useful in this context. Note that the regulation was revised to have additional categories of evidence for bioaccumulation that should cover metal compounds. The prioritization and alternatives assessment processes, which are the subjects of a regulation being developed by DTSC, are outside the scope of this regulation.

44f. Comments on Section 69405.3 – Environmental Persistence

A commenter objected to the inclusion of environmental persistence as a hazard trait:

> "… [P]ersistence is not a hazard characteristic. Persistence is a characteristic whereby the chemical resists photolytic, biological and chemical degradation. Because it is persistent, a material could become measurable in environmental media and depending on the level, it may be present in high enough concentrations to [r]each an effect level for organisms that are exposed; however, persistence in itself is not a hazard trait. OEHHA should include persistence as "other relevant data" as it is a common chemical measure." (GCA)

A comment notes that there are a number of types of data that should be included in the Clearinghouse:

> "…Rates of degradation of a substance in the environment are determined by a combination of substance specific characteristics and environmental conditions. … However, we acknowledge that there are a number of widely accepted standardized test methods that measure the half-life of a chemical, typically under laboratory conditions…It is appropriate for OEHHA to include biodegradability data, aerobic and anaerobic transformation data and other related data in the "other relevant data" portion of the TIC." (ACI)

One comment suggested a change to the regulation's description of evidence of environmental persistence:

> "In the Environmental Persistence definition (Section 69405.3, page 22), the list of evidence of persistence allows only persistence in marine (salt water) sediments to count--fresh water or estuarine sediment persistence would not count as evidence. This inappropriately de-values fresh and estuarine water bodies. The solution is to delete the word "marine", so that it would read "Evidence for environmental persistence includes half-lives in marine, fresh, or estuary water of greater than 40 to 60 days, in [deleted: marine] sediment for greater than 2 months, ..." (Sierra Club)

Response: OEHHA disagrees that persistence is not a hazard trait. It is an oft-measured or estimated characteristic because it contributes to the overall hazard of a chemical. Persistence of a chemical in the environment promotes sustained exposure and contributes to accumulation in the environment. Because persistence is an inherent property of a chemical in the environment that results in increased exposure to the chemical and consequently potential for health risks, it can appropriately be identified as a hazard trait. Legacy chemicals such as DDT and PCBs remain public health concerns decades after their production was banned because of their ability to persist in the environment. OEHHA believes viewing a chemical's persistence as "other relevant data" would inappropriately downplay these kinds of concerns. Thus, persistence is being specified as a hazard trait for inclusion in the Toxics Information Clearinghouse. No change to the regulation was made based on this portion of the comment.

OEHHA inadvertently left out fresh-water sediments when describing the half-life of chemicals in sediments as evidence of persistence. To address this problem the word "marine" in front of sediment was deleted, thereby including marine, estuarine, and freshwater sediments. No other changes to the regulation were made based on these comments.

44g. Comment: A comment recommends that text be added to the sections on environmental persistence in the regulation as follows:

> "Persistence is problematic as a hazard trait for metals because -- while all metals and other elements on the periodic table are conserved and, hence, persistent -- the form and availability of the metal can change (thereby affecting its potential toxicity) depending on the environmental conditions. The nature of these changes and the environmental conditions under which they occur are different for each metal element and must be considered on a metal-by-metal basis." (NAMC)

Response: OEHHA agrees that the form of a metal compound and its availability influence toxicity. OEHHA also agrees that metals by nature are persistent because they are not degraded like most organic compounds. These considerations, however, are not relevant to this regulation, as this regulation does not prescribe how the information contained in the clearinghouse is to be used. These considerations will be taken into account in DTSC's evaluation of whether a chemical has a hazard trait. No change to the regulation was made based on this comment.

44h. Comments on Section 69405.4 – Global Warming Potential (GWP)

> "Global Warming Potential (GWP) is not a hazard trait and should therefore be removed from the regulation." (GCA)

Response: OEHHA disagrees with this comment. A number of state, national and international regulatory agencies have promulgated or are in the process of attempting to promulgate regulations to control emissions of greenhouse gases because of their contribution to global warming. The global warming potential is an inherent property of a chemical substance that contributes to harmful, increased warming of the planet. Global warming may cause adverse effects in some or all of the categories specified in the definition of hazard trait: "exposed humans, domestic animals, wildlife, or in ecological communities, populations or ecosystems".

There is a broad consensus among scientists that global warming related to the emissions of greenhouse gases is a paramount environmental concern that must be addressed. Thus, information concerning the potential for a given chemical to contribute to global warming should be included in the Clearinghouse. No change to the regulation was made based on this comment.

44i. Comments on Section 69405.6 – Mobility in Environmental Media

> "Mobility in environmental media is not a hazard trait and should therefore be removed from the regulation. Mobility in air, water or soil/sediment will depend on external conditions, such as temperature, humidity, organic content of soil and sediment. Mobility is not an inherent characteristic of a chemical and it is not a hazard trait." (GCA)

Another comment had suggestions regarding specific evidence for environmental mobility.

> "The qualitative evidence for this trait is given, but no specific quantitative criterion is specified - for example, based on log Pow, Koc, ionic charge density, etc. It is suggested that such quantitative criteria could be adapted from US EPA, REACh, etc and be incorporated into the current regulation." (Dow)

Response: OEHHA disagrees that mobility in environmental media is not an exposure potential hazard trait. Mobility in environmental media is an inherent property of a chemical that results in widespread distribution of a chemical throughout the environment and contributes to higher probability of human and wildlife exposures. The

fuel additive MTBE was banned in California and elsewhere because of its mobility in groundwater.
OEHHA appreciates the information provided in the comments regarding potential information relevant to assessing mobility in environmental media. DTSC, pursuant its mandate under AB 1879, will have the authority to decide whether or not a chemical substance has a hazard trait. Thus, the suggestions in the comments may be useful to DTSC's processes.

No change to the regulation was made based on this comment.

44j. Comments on Section 69405.7 – Particle Size or Fiber Dimension

.Some comments raise the concern that size alone should not be considered an intrinsic hazard:

> "If Article 5 is not deleted in its entirety, Section 69405.7 is uniquely inappropriate because it wrongly perpetuates the inaccurate perception that a chemical substance is intrinsically hazardous due solely to its size, regardless of exposure considerations. This is scientifically indefensible and uniquely stigmatizes nanoscale materials." (SOCMA)

> "By themselves, particle size and fiber dimension do not convey hazard, only deposition probability in the respiratory tract, and therefore inclusion of this separate category as a "hazard trait" is inappropriate and misleading." (GCA)

GCA and CalNIN also expressed concern that Section 69405.7 also includes "dermal or ingestion exposure." The comments note the reference to other routes is confusing and should be stricken. They stated concern that if there is no exposure there is no hazard. For instance,

> "According to the Statement of Reasons, the express intent of this is to focus on particles which may pose respiration hazard – clearly airborne nanomaterials can be respirable. However, the trait definition, itself, seems not narrowly tied to respiration. If opportunities for release are minimal or zero, the provision doesn't apply." (GCA)

GCA and CalNIN stated that particle and fiber dimension is appropriately included in the "other relevant data" section (Section 69403.15) of the respiratory toxicity hazard trait.

It was also noted that the use of the term “small particle” in Section 69405.7 is confusing with respect to nanoparticles “which have the propensity to form larger particles through agglomeration or aggregation” (CalNIN). The need to refine the definition of small particle was noted.

Response: The purpose of the particle size and fiber dimension exposure potential hazard trait, as explained in the ISOR, page 114, is to recognize that a chemical substance can either be manufactured as very small size particles, or form small particles upon release (e.g., as an airborne emission from an industrial process) and that particles smaller than a particular size can be inhaled. Many non-volatile or semi-volatile substances exist as very small particles in the air. Some chemicals are manufactured as very small particles and could be released from consumer products. These tiny particles can readily access the deep lung when inhaled, and cross biological barriers including the lung or the gut when ingested, and broken skin when contacted dermally. Thus exposure to chemicals in these small particles can be larger than exposure when the chemical is in the form of larger particles (bulk form), which cannot access the deep lung or readily cross biological membranes. The particle size and fiber dimension of concern is spelled out in Section 69405.7 (b) in the regulation.

No change to the regulation was made based on this comment.

Comment:

> “The definition cites a “3:1 aspect ratio” as relevant to considerations relating to potential hazard. This is incorrect unless the particle or fiber is at least 1 micron in diameter. A recent article by Sturm and Hofmann (J. Haz Mater 170, 210-218, 2009) looked at the impact of aspect ration for fibers of varying diameter (CNTs up to asbestos). Their calculations show that an aspect ratio of 3 has an impact only when the diameter is at least 1 micron. In fact, even an aspect ratio of 100 has little impact on the aerodynamic diameter for a fiber of 1 nanometer diameter. This is aside from any biological effect, for which we already have some experimental data (Poland et al, 2008; Muller et al, 2009 ; Porter et al, 2010) to demonstrate length-dependent effects.” (CalNIN)

Response: The “3:1 aspect ratio” cited in the comment is not part of the definition of the hazard trait, but is instead guidance indicating that an aspect ratio of 3:1 for a fiber is evidence that the fiber poses a potential exposure hazard. The aspect ratio of 3:1 is derived from standard regulatory guidelines for occupational exposure to fibers.
This is an area of active research and was the subject of a 2009 National Academy of Science report: A review of the NIOSH Roadmap for Research on Asbestos Fibers and

Other Elongate Mineral Particles. The committee found the dimensions described in the NIOSH roadmap (longer than 5 µm with a minimum 3:1 aspect ratio) encompassed the respirable range.

OEHHA recognizes that there are many types of fibers with various degrees of toxicity. For asbestos, there is considerable epidemiological data that longer asbestos fibers may be more dangerous in term of cancer-causing potential than shorter fibers. But the shorter fibers are not innocuous. Further, the width of a fiber does not have to be 1 micron to be problematic. Much smaller asbestos fibers can be found in the lung and mesothelial tissues of asbestos-exposed individuals. The comment states that "even an aspect ratio of 100 has little impact on the aerodynamic diameter of a 1 nanometer diameter fiber". A I nanometer fiber with such a large aspect ratio would be able to enter the lung readily. The ISOR contains additional references and there is a considerable literature on the topic of particle size. The regulation provides guidance and ultimately the decision regarding whether or not a particular chemical has a hazard trait is DTSC's, as discussed in response to comments 4 and 5 above.

No changes were made to the regulation based on this comment.

Comment:

> "MMAD [mass median aerodynamic diameter] may not be best method for "small" particles…. It would be inappropriate for materials to be classified under this hazard trait based on MMAD calculated indirectly from the primary particle size rather than the actual measured aerosolized diameter. Dispersed materials are frequently in an aggregated or agglomerated format. Using a calculated MMAD based on mass distribution of primary particle size may result in large aggregates and non-respirable particles being classified under this hazard trait. This type of quantification could lead to unrealistic classification of nanomaterials, which are not typically present in respirable fractions because they are agglomerated (>10 um MMAD)." (CalNIN)

Response: The comment may be correct. However, no alternative method to provide a cut-off point for particle size was offered. Rather a hypothetical exposure scenario is described where the released nanoparticles have agglomerated to the point that they are non-respirable (e.g., larger than 10 um in MMAD).

The regulation simply provides guidance on evidence that is indicative of a hazard trait. Ultimately it is DTSC's decision on whether or not a chemical substance has a hazard trait. While this regulation does not encompass this type of an exposure assessment

issue, DTSC pursuant to AB 1879 can also take into account a number of factors that fall outside this regulation.

No change to the regulation was made based on this comment.

Comment: CDPH commented regarding the particle size and fiber dimension hazard trait: "Consistent with comments made above (under Respiratory Toxicity), we recommend that 69405.7(a) use the term "inhalable particles" rather than the vague and undefined "small particles" or "small-sized particles."
69405.7(b) as written implies that only particles less than or equal to 10 micrometers in mass median aerodynamic diameter can have health consequences due to inhalation exposure. This is incorrect, and again, under the same rationale as discussed above, this section should be revised to include measures of "inhalable" particle sizes ranging up to 100 micrometers as evidence for relevant inhalation exposure. Although particles larger than the smaller-size fraction defined as "respirable" will in some cases not be relevant to health risk (e.g., particles containing crystalline silica will only cause silicosis if they deposit in the alveolar region of the lung), there will be other chemicals that pose a hazard when present in inhalable particles as large as 100 micrometers.

> "There is a rapidly growing expansion in the use of chemical substances in the nano-sized range, because of the unique properties conferred by these minute particle sizes. This is an area where only limited information on toxicity currently exists, and the emergence of new information categorized as such would be very helpful. We suggest that OEHHA specifically name particle size in the nano-range as a separate consideration under this section of the regulations, similar to the way the unique hazard of fibers is highlighted."

Response: The regulation does not state that the only particles that can have toxicity are those 10 µm or less in diameter. As noted in response to comment 30c, the comment is correct in saying that chemicals in inhalable particles larger than 10 µm can be associated with toxicity as they may affect the nose, mouth and upper airways or be deposited and swallowed. Chemicals exhibiting those types of toxicity would be covered under respiratory toxicity and other hazard traits although they are not called out in this section on exposure potential hazard traits. In the ambient environment, the concern is generally with very small particles that can get deep into the lung. Thus, while chemicals carried on larger particles can induce toxic effects, in terms of the typical ambient environment, there is greater concern for toxicity from small particles entering the deep lung. Note that the endpoints listed are nonexclusive and the evidence of toxicity to the nasal or oral epithelium or upper airways should be considered when evaluating chemicals for this hazard trait.

In regard to specifying nanoparticles, the particle size hazard trait would include nanoparticles as they are smaller than 10 µm in diameter.

No changes to the regulation were made based on these comments.

44k. Comment on Section 69405.8 – Stratospheric Ozone Depletion Potential

> "Stratospheric Ozone Depletion Potential (ODP) is not a hazard trait and should therefore be removed. According to EPA's Ozone Layer Protection Glossary "Ozone Depletion Potential (ODP): a number that refers to the amount of ozone depletion caused by a substance. The ODP is the ratio of the impact on ozone of a chemical compared to the impact of a similar mass of CFC-11. Thus, the ODP of CFC-11 is defined to be 1.0. Other CFCs and HCFCs have ODPs that range from 0.01 to 1.0." (GCA)

Response: Stratopheric ozone depletion is a hazard trait because the ozone layer protects life on earth from harmful UV rays. Its depletion leads to more cases of skin cancer, cataracts, and a number of effects on the planet's biota. Chemicals that deplete the ozone contribute indirectly to these adverse effects. For this reason, there have been many state and federal regulatory actions to lower the emissions of chemicals that deplete the stratospheric ozone layer. The GCA comment notes that US EPA can quantify a chemical's ability to deplete stratospheric ozone. This would appear to support OEHHA's view that a chemical's ability to deplete stratospheric ozone is an inherent property that should be considered a hazard trait.

The regulation provides that "…listing as a chemical substance in the Montreal Protocol or U.S. EPA pursuant to Section 612(a) of the Clean Air Act as a substance that depletes stratospheric ozone" is an example of evidence that a substance has the ozone depletion hazard trait. As noted in the ISOR, under the Clean Air Act, U.S.EPA has banned production and import of stratospheric ozone depleting substances and established a list of acceptable substitutes. The European Union also has regulations concerning the labeling of ozone-depleting substances. No change to the regulation was made based on this comment.

44l. Comment on adding a trait "biologically-based exposure potential" to the list of exposure potential hazard traits: PCRM suggests adding biologically-based exposure potential as a hazard trait in Article 5. They would include the potential for a substance to penetrate the blood-brain barrier, the skin, or the lining of the gut and

airways. They note that these traits are intrinsic and impact whether and to what degree a substance might cause toxicity.

Response: To a large extent, the factors that drive absorption across a biological surface (lung, gut, skin) following contact are determined by the physico-chemical properties of a compound. The regulation was modified to include these properties in Article 7. The idea of including this as a hazard trait is meritorious, but the exposure potential hazard traits emphasize characteristics that provide the potential for hazardous external exposures. The factors in the proposed trait are covered by considerations of the physico-chemical properties of a chemical, and may be especially pertinent as other relevant data for the toxicity hazard traits. For example, data indicating a chemical may penetrate the blood-brain barrier may be pertinent to the evaluation of its potential to cause central nervous system toxicity and possess the neurotoxicity hazard trait.

No changes to the regulation were made based on this comment.

45. Comments on Article 6 - Physical Hazard Traits

Comment: A comment called for the regulation to include US-based criteria for flammability:

> "Flammability is proposed to be identified as a hazard by reference to criteria in sections of the United Nation's Globally Harmonized System for the Classification and Labeling of Chemicals (GHS). This proposal fails to recognize that regulatory systems specifying criteria for flammability exist in the U.S., such as those of EPA, OSHA and CPSC. OEEHA would create confusion and added burden by calling for a different criterion than those that are already routinely being applied by U.S. regulators and manufacture…ACI urges OEHHA to revise the criterion for flammability to reference existing U.S. regulatory criteria and remove references to the GHS." (ACI)

Response: In response to this comment, a provision was added to the regulation that evidence for flammability includes meeting the definition of the Occupational Safety and Health Regulations 29 CFR Part 1910 Subpart Z Toxic and Hazardous Substances Standard Number 1910.1200.

Comment: Another comment from CDPH requested that Corrosivity and Radioactivity be added as hazard traits to the regulation.

Response: We understand the concern for both radioactive materials and corrosive materials. Radioactivity is encompassed in our definition of "chemical substance", so radioactive chemicals are captured by this regulation. Further, ionizing radiation is an example of reactivity in biological systems as ionizing radiation causes damage to cellular macromolecules including DNA. Radioactive materials are widely studied and have been well characterized in terms of toxicity, and have ample evidence to consider in the assignment of toxicological hazard traits.

Corrosivity is also captured by various toxicological hazard traits. The comment specifically noted concern for acids and bases. Strong acids and bases can cause serious tissue damage by destroying cellular structure and thus would fall under the hazard trait "reactivity in biological systems", and other toxicological hazard traits depending on the organ or tissue affected (e.g., respiratory tract toxicity, dermatotoxicity).
No changes were made to the regulation based on this comment.

SUMMARY AND RESPONSE TO COMMENTS RECEIVED DURING THE COMMENT PERIOD OF JULY 29, 2011 THROUGH SEPTEMBER 12, 2011.

OEHHA received comments from the following groups or individuals:

American Chemistry Council (ACC)
American Cleaning Institute (ACI)
Bay Area Clean Water Agencies and Bay Area Pollution Prevention Group (BACWA/BAPPG)
California Association of Sanitation Agencies (CASA)
California Industrial Hygiene Council (CIHC)
Californians for a Healthy and Green Economy (CHANGE)
Cradle to Cradle Products Innovation Institute (CCPII)
Dr. Lauren Heine of Clean Production Action
The Dow Chemical Company (DOW)
Dr. Amy Kyle of University of California at Berkeley, School of Public Health
E.I. DuPont de Nemours and Company (DuPont)
Global Automakers
Grocery Manufacturers Association (GMA)
Green Chemistry Alliance (GCA)
North American Insulation Manufacturers Association (NAIMA)
Rubber Manufacturers Association (RMA)

Many of the comments received were not on the July 2011 proposed modified text, or on the procedures used to propose it, but instead were on the December 2010

proposed regulation. Thus, pursuant to Government Code section 11346.9(a)(3), OEHHA is not responding to those comments here. However, the majority of those comments raise the same issues that were raised in comments on the December 2010 proposed regulation, and are addressed in responses to those comments.

Summarized below are the comments pertaining to the first modified text of the proposed regulation and OEHHA's responses.

1. Comment:

"The independent external scientific peer review of the scientific basis of Proposed Rulemaking Title 22, California Code of Regulations, § 69401 - § 69406 Green Chemistry Toxics Information Clearinghouse Identification of Hazard Traits, Endpoints and Other Relevant Data for Inclusion in the Toxics Information Clearinghouse (December 2010), and OEHHA's response to the peer review, were insufficient to comply with requirements of California Health and Safety Code § 57004.

"On June 17, 2011, OEHHA posted peer review comments submitted by three peer review scientists (Pertti Hakkinen, Ph.D. of the National Institutes of Health; Bette Meek, Ph.D., of the University of Ottawa; and Errol Zeiger, Ph.D., of Errol Zeiger Consulting). Examination of the peer review comments, however, indicates that although the peer reviewers are respected experts in their disciplines, they lacked expertise to comment on all aspects of the proposed regulations (see statements by the peer reviewers themselves). In fact, the peer reviewers did not comment on all of the Articles.

"NAS [National Academy of Sciences] is the ideal body to conduct the peer review; however, if this is not possible, the state should reconvene a panel according to HSC § 57004, with the appropriate expertise."

(ACC, similar comments by GCA, ACI, and DOW)

Response: The peer review of this regulation fully complied with the requirements of Section 57004. The California Environmental Protection Agency (Cal/EPA) has entered into a Memorandum of Understanding (MOU) with the UC Office of the President for the purpose of obtaining peer reviews as required by Health and Safety Code §57004. The MOU covers the peer reviews for all of the Cal/EPA boards, departments and office; the statute does not require OEHHA to use the NAS for review of this proposed regulation, and OEHHA believes that a second peer review by the NAS or any other entity is unnecessary. The three peer reviewers were carefully selected by the UC Office of the President. The peer reviewers were experts in hazard identification and chemical classification and provided useful input on the regulation. Each of the peer reviewers

reviewed the proposed regulation and the ISOR and submitted written comments, as required by Section 57004.

No changes to the proposed modified text of the regulation were made based on this comment.

2. Comment:

"Although OEHHA added a new entry in Article 7, labeled "Exposure-Response Relationship" (§69407.1), the text there does not indicate the importance of such information to the hazard identification process." The context for this comment was that the "proposed regulations does not consider dose or potency as an initial step in the evaluation of hazard traits," and that the modified text did not go far enough. (ACC)

Response: Several comments on the proposed regulation asked that the regulation specifically identify potency information as other relevant data in the Clearinghouse so that it could be used for prioritization by DTSC. Article 7 Section 69407.1 in the Modified Text was added to recognize potency data as relevant for inclusion in the Clearinghouse. OEHHA noted in response to earlier comments that while potency is important for prioritization, this regulation does not prioritize chemicals, nor does it assign hazard traits to specific chemicals. DTSC is responsible for evaluating, identifying and prioritizing chemicals, and therefore this regulation does not specify how potency or related information should be used in evaluating chemicals.

No additional changes to the regulation were made based on this comment.

3. Comment:

"In § 69401.1 of the proposed regulation, OEHHA changed the wording from "… requires the Department of Toxic Substances Control (hereafter referred to as "Department" or "DTSC") to evaluate chemicals by developing criteria…" to "… requires the Department of Toxic Substances Control (hereafter referred to as "Department" or "DTSC") to develop criteria for chemical evaluations…" With this proposed change of wording, it is unclear what entity within California government will be conducting the chemical evaluations. What DTSC envisions, and how DTSC will assure consistency in evaluation of the same chemical if DTSC is not conducting such evaluations is unknown." (ACC, similar comment by GCA)

Response: The change in Subsection 69401 makes the provision consistent with the language in AB 1879 requiring DTSC's to identify, prioritize and regulate chemicals of concern in consumer products. In addition to DTSC's chemical evaluations, AB 1879 also allows businesses to evaluate chemicals as part of their alternatives assessments. The language in the initial draft of OEHHA's regulation was potentially confusing, and

was clarified in the amended text. No additional changes to the regulation were made based on this comment.

4. Comment:

"…the regulations would require new duties of the state in that individual classification of chemicals would be required. For example, the modified proposed regulations include a new neurodevelopmental toxicity hazard trait (Section 69403.11)." (ACI)

Response:

The proposed regulation does not require individual classification of chemicals, including those exhibiting neurodevelopment toxicity. Rather it identifies the types of information that should be included in the Clearinghouse, and provides guidance on how certain types of information can be used to identify a hazard trait. How that information may be used by DTSC or others is beyond the scope of this regulation. This issue is further discussed in the responses to comments on the December 2010 version of the proposed regulation.

No changes to the regulation were made based on this comment.

5. Comment:

"In response to their obligations under California Government Code Section 11346.5(a)(13), OEHHA indicated on page 6 of the Notice of Proposed Rulemaking that "no reasonable alternative considered by OEHHA, or that has otherwise been identified and brought to the attention of OEHHA, would be more effective in carrying out the purpose for which the action is proposed or would be as effective and less burdensome to affected private persons than the proposed action." In our February 15, 2011 comments on the proposed regulations we proposed several other reasonable alternatives that would be more effective and less burdensome in carrying out the purpose of the proposed action." (ACI)

Response: OEHHA carefully considered the February 15, 2011 comments and suggested alternative language and approaches and found some of them to have merit. These changes were included in the July 2011 modified proposed text. For example, in response to ACI's comments, the July 2011 version included criteria used in the United States (29 CFR Part 1910) as evidence of the flammability hazard trait.

Some of the alternatives suggested by ACI would have made the regulation insufficiently comprehensive to offer a complete compilation of hazard traits, endpoints and other relevant data for purposes of the Clearinghouse. OEHHA's responses to the specific alternatives offered by ACI and other comments are discussed in the responses to comments on the December 2010 version of the regulation.

No additional changes to the proposed modified text of the regulation were made based on this comment, but the record was augmented to include information supporting the change in § 69406.3 Flammability.

6. Comment:

"The amended proposed definition of "hazard traits" remains unclear and should be replaced or, at a minimum, be made consistent with existing Federal definitions. The modified definition of "hazard traits" does not sufficiently clarify the meaning of the term. We note that OEHHA has proposed a new unique term rather than relying on existing terminology that has been used for decades." (ACC, similar comment by GCA)

Response: The term "hazard traits" was coined in SB 509, the legislation that directed OEHHA to specify the information to be included in the Toxics Information Clearinghouse. There is no existing Federal definition of "hazard trait". This and other comments also confuse the commonly used term "hazard" with "hazard trait". The regulation does not identify any chemical as hazardous, does not classify chemicals and is not in conflict with any hazard classification systems currently in use. No changes to the regulation were made based on this comment.

7. Comment:

"The amended proposed regulations improperly include arbitrary assignment of some physicochemical properties as Exposure Potential Hazard Traits and others as Additional Relevant Data… The amended proposed regulation includes a new section on Additional Relevant Data which includes a number of physicochemical properties. The "exposure potential" hazard traits would be better included in those properties." (ACI)

Response: OEHHA disagrees. The organization of the regulation is not arbitrary. The physicochemical properties of a compound impact exposure as they affect whether or not a chemical can bioaccumulate or move into water or air, and provide evidence that the chemical has the exposure potential hazard trait. For example, § 69405.2, which identifies Bioaccumulation an exposure potential hazard trait, refers to a non-exclusive list of evidence for bioaccumulation which includes log-octanol water and log octanol-air partition coefficients found to be above certain values. These measurable properties are related to bioaccumulation and can be used to estimate bioaccumulation in the absence of other data. These measurements are used by national and international bodies as evidence for bioaccumulation, as indicated in the ISOR (pages 110-111), and in the reference[7] added to the record in the October 7, 2011 Notice of Augmentation to the

[7] Gobas FAPC et al. Revisiting bioaccumulation criteria for POPs and PBT assessments, Integrated Environmental Assessment and Management, Volume 5, Number 4, pages 624-637, 2009.

Record. Thus, they are appropriately referred to under the bioaccumulation hazard trait. These and many other physicochemical properties are also useful in evaluating the fate of chemicals in products and the environment and are thus appropriately listed in additional other relevant data in Article 7.

OEHHA disagrees with ACI's argument that exposure potential hazard traits should instead be included in the regulation as "additional relevant data" in Article 7. OEHHA responds to similar comments in the response to comments on the December 2010 version of the regulation. Exposure potential traits such as bioaccumulation, environmental persistence, ambient ozone formation, global warming potential, mobility in environmental media and the others identified in the regulation are inherent properties of a chemical that can increase the potential for exposure to the chemical in humans and animals. As inherent properties of chemicals, they meet the regulation's definition of "hazard traits" and should be recognized as hazard traits in DTSC's consumer-products regulatory program. For decades, regulatory agencies in California and throughout the world have developed programs and enacted regulations to reduce releases of these chemicals.

No changes to the regulation were made based on this comment, but the record was augmented to include an additional reference for bioaccumulation.

8. Comment:

"We appreciate the changes made in Sections 69404.3 and 69405.3, with regard to wastewater treatment organisms and processes, and environmental persistence of chemicals in fresh, estuarine and marine waters and sediments." (BACWA, CASA)

Response: Comment noted. The comment indicates agreement with changes reflected in the Modified Text that were made in response to their previous comments on the December 2010 version of the proposed regulation.

9. Comment:

"Our only suggestion for improving the draft would be to change the project heading "Green Chemistry Hazard Traits". The title is incongruous with widely-accepted definitions of "green chemistry." The comment goes on to suggest changing the title of the regulation to "Toxics Clearinghouse Hazard Traits." (CCPII)

Response: In response to this comment, the title of the regulation has been changed to "Green Chemistry Hazard Traits for California's Toxics Information Clearinghouse"

10. **Comment:**

Certain comments agree with the addition of the neurodevelopmental hazard trait to the regulation given the impacts on infants and children and also support the addition of Article 7, ”Additional Relevant Data.” (CHANGE, Dr. Kyle)

However, CHANGE expresses concern that by including exposure-response information in the Clearinghouse, “the TIC may be used to weight the value of data in a risk assessment framework, which is not a function the TIC has been mandated to perform.” The comment goes on to say hazardous chemicals may continue to be used because of weaknesses in the exposure-response data.

Response: Comment noted. The neurodevelopmental hazard trait was added in response to several comments on the December 2010 proposed regulation. Article 7, Subsection 69407.1 “Exposure-Response Relationships” was also added in response to comments that information on the potency of a chemical to induce toxicity is important information to have in the Toxics Information Clearinghouse. While it may be encompassed by information on the toxicological endpoints for a variety of the hazard traits, there should be specific mention of exposure-response data in the Clearinghouse and thus this subsection was added. The Clearinghouse is a repository of information. The Clearinghouse does not classify chemicals as having specific hazard traits, and is not a risk assessment framework. No changes to the proposed regulation were made based on this comment.

11. Comment:

OEHHA has identified bioaccumulation as a hazard trait, but the definition does not seem to include specific organ accumulation. (Dr. Heine)

Response: The definition in subsection 69405.2(a) includes accumulation of a chemical in tissues of an organism, and subsection 69405.2(b) explains that evidence of bioaccumulation includes “studies which show bioaccumulation in human, domesticated animal, wildlife, or plant tissues”. Thus accumulation in a specific organ is included in this definition. No changes to the regulation were made based on this comment.

12. Comment:

One commenter notes that edits throughout the text have been made to make it more consistent and understandable (Dr. Kyle). Another commenter (GCA) objected to clarifying edits of “including but not limited to” in sections 69405.3 to 69405.5

[Environmental Persistence, Global Warming Potential, Lactational or Transplacental Transfer] as providing too much "subjective authority to OEHHA and DTSC" and that hazard traits should list the types of data or criteria that will be considered. The GCA recommends removing the phrase "including but not limited to" from other parts of the regulation as well.

Response: OEHHA made clarifying edits to increase consistency throughout the regulation in use of certain words. In particular, with regard to the phrase "including but not limited to," as explained in the Statement of Reasons, it is impossible to identify and list all types of scientific evidence relevant to a specific hazard trait in a regulation. First, there are many different types of data that could be weighed as evidence for a specific hazard trait. Second, new toxicity tests and other scientific approaches are evolving all the time. Thus, it is logical to describe non-exclusive lists of the types of endpoints and other relevant data that may indicate the presence or absence of a hazard trait for any specific chemical. Hence the phrase "including but not limited to" is included throughout this regulation to underscore this fact. In doing so OEHHA recognizes that the term "includes" already implies that the list that follows is non-exclusive. The words "but not limited to" merely provide greater clarity.

While the list of "authoritative organizations" does not include the words "but not limited to" in section 69401.2(b), that list is not meant to be exclusive and any organization meeting the definition of "authoritative organization" is intended to be part of the list, as explained in the Initial Statement of Reasons (ISOR) (page 4).

No changes to the regulation were made based on this comment.

13. Comment:

The amendments to the definition of authoritative organization "continue to raise the concern that the definition fails to account for the concept of deliberative review." (GCA) The proposed regulation was modified to explicitly note as an authoritative organization "environmental and public health regulatory agencies of other states." (Page 4 of the July 2011 first Modified Text). The commenter objects to continuing to refer to agencies from other states as authoritative organizations as these entities may have no authoritative scientific processes in place.

Response: The definition in Subsection 69401.2(b) contemplates a deliberative process. The definition is "Authoritative organization means a state, national, international or nongovernmental entity whose scientific findings on the safety, risks or hazards of chemical agents are relied upon by the state, national or international governments and their supporting public health or environmental entities in regulating or

otherwise protecting human health or the environment from threats posed by those chemical agents."

As explained in the ISOR, Subsection 69401.2(b) defines "authoritative organization," in terms of how the scientific findings of authoritative organizations are used. It restricts the identified entities to those organizations that provide the scientific basis for formal public health protections by government entities.

Subsection 69401.2(b) identifies a non-exclusive list of governmental and non-governmental institutions that satisfy the definition of "authoritative organizations," including California agencies. The legal and administrative processes applied by these agencies help ensure the validity of the scientific documents supporting California public health and environmental regulations and guidance. Other organizations listed in the regulation have procedures in place, including peer review, data quality and scientific guidance that ensure the scientific integrity of work products produced for regulatory and public health purposes.

For example, the World Health Organization includes the International Agency for Research on Cancer, an organization renowned and widely respected for its evaluation of the potential carcinogenicity of chemicals that uses expert review and deliberation. The International Programme for Chemical Safety publishes the report series "Environmental Health Criteria Monographs," that are relied upon by other nations and organizations for decision-making. The United Nations houses the World Health Organization, organizations that developed the Globally Harmonized System of Classification and Labeling of Chemicals, the International Labor Organization and other organizations that provide expert evaluations of chemical hazards. Thus, we have incorporated the expectation of deliberative review in this regulation. The regulation does not require anyone to give deference to the findings of any authoritative organization. The regulation identifies various sources of information, including these authoritative organizations, whose conclusions are information to be included in the clearinghouse. The various classification criteria, rules or methods used by these organizations are readily available to the public and are generally discussed in the documents that would be included in the Clearinghouse. How DTSC or others might view the relevant findings of such bodies is speculative and beyond the scope of this rulemaking. No changes to the regulation were made based on this comment.

14. **Comment**:

OEHHA has not been expressly delegated authority to promulgate regulations. (GCA)

Response: OEHHA disagrees with the comment's implication that it lacks the authority to promulgate this regulation. Health and Safety Code Section 59012 provides general

authority for OEHHA "to adopt and enforce rules and regulations for the execution of its duties." Furthermore, the Administrative Procedure Act (APA) requires OEHHA to fulfill its SB 509 mandate by promulgating a regulation.

SB 509 requires OEHHA to "…evaluate and *specify* the hazard traits and environmental and toxicological end-points and any other relevant data that *are to be included* in the clearinghouse." (Health & Safety Code section 25256.1, emphasis added)
The APA requires agencies to use the regulatory process when issuing or adopting:

> " … every rule, regulation, order, or standard of general application or the amendment, supplement, or revision of any rule, regulation, order, or standard adopted by any state agency to *implement, interpret, or make specific the law* enforced or administered by it, or to govern its procedure. (Government Code section 11342.600, emphasis added)

Conversely, an "underground regulation" is defined as:

> "(a) …any guideline, criterion, bulletin, manual, instruction, order, standard of general application, or other rule, including a rule governing a state agency procedure, that is a regulation as defined in Section 11342.600 of the Government Code, but has not been adopted as a regulation and filed with the Secretary of State pursuant to the APA and is not subject to an express statutory exemption from adoption pursuant to the APA." (Title 1, Cal Code of Regulations, section 250(a))

OEHHA is implementing, interpreting and making specific the requirements of SB 509 by specifying the information that is to be included in the Clearinghouse that will be developed by DTSC. Therefore, it must adopt its scientific guidance concerning the content of the Clearinghouse via the APA process. Further, using the APA regulatory process ensures a transparent process that is open to anyone who chooses to participate and creates a permanent administrative record for the action.

In response to this and other comments, OEHHA is explicitly including its general authority to adopt regulations as a supplement to the authority already cited in the regulation. No other changes to the regulation were made based on this comment.

SUMMARY AND RESPONE TO COMMENTS RECEIVED DURING THE COMMENT PERIOD OF OCTOBER 07, 2011 THROUGH OCTOBER 24, 2011.

OEHHA received comments from the following groups or individuals:

American Chemistry Council (ACC)

American Cleaning Institute (ACI)
Californians for a Healthy and Green Economy (CHANGE)
Green Chemistry Alliance (GCA)
Global Automakers (GA)

Many of the comments received did not address the proposed changes to the regulation that were the subject of the 15-day Notice, or the procedures used to propose it.. Instead they repeated comments submitted on the December 2010 version of the proposed regulation. Thus, pursuant to Government Code section 11346.9(a)(3), OEHHA is not responding to those comments here.

Summarized below are the comments pertaining to the changes contained in the October 7, 2011 version of the proposed regulation and OEHHA's responses:

1. **Comment**:

"Revising Section 69401.1 by adding the phrase "to be included in the Clearinghouse" is insignificant and does not clarify the intent with regard to implementation of the regulation. "(ACC and GCA)

Response: This phrase was not added to clarify the intent with regard to implementation of the regulation, but more closely reflects the requirements of Health and Safety Code section 25256.1. No changes to the regulation were made based on this comment.

2. **Comment**:

"GCA is highly concerned regarding the addition of the word "potential" in relation to the presence of a hazard trait. The addition appears to direct the hazard trait framework toward a more precautionary approach effort. Such a change is highly objectionable, as the framework is supposed to be based in and rely on evidence-based, sound scientific principles. This is inconsistent with the intent of the enacting statutes, which require that the framework be based in sound science rather than precaution."

Response: The comment refers to a sentence in Section 69401.1 that describes other relevant data as follows: "These data can be observed through scientific study and provide less-direct but useful evidence of the potential presence of a hazard trait." Non-exclusive lists of different types of other relevant data are included in the regulation for toxicological and environmental hazard traits. The addition of the word "potential" in front of "presence of a hazard trait" clarifies that the other relevant data may indicate, rather than definitely indicate, the presence of a hazard trait. Note that this regulation

does not classify any chemical as having or not having a hazard trait. Rather, the regulation identifies the types of information (hazard traits, toxicological and environmental endpoints, and other relevant data) to be included in the Toxics Information Clearinghouse. No change was made in the regulation in response to this comment.

SUMMARY AND RESPONSE TO PEER REVIEWS

Response to Comments from Dr. Pertti Hakkinen

Pertti (Bert) J. Hakkinen, Ph.D. Senior Toxicologist, and Toxicology and Environmental Health Science Advisor (to the Director) Specialized Information Services, National Library of Medicine, National Institutes of Health (representing himself)

1. Accuracy and clarity of the definitions presented (Article 1, Section 69401.2 in the proposed regulation and Section V, Article 1, Section 69401.2 in the Initial Statement of Reasons).

Comment: The definitions presented are judged to be both accurate and clear in both documents. The only comment I have is that the "that negatively affects" wording could be changed to "could negatively affect." This suggested change is based on noting that an actual impact on performance or ability to respond could depend on the "reserve capacity" of the individual organism for that trait or endpoint versus the actual magnitude of the exposure and effect.

Response: The comment refers to the definition of adverse effect in Section 69401.2, which is as follows: " 'Adverse effect' for toxicological hazard traits and endpoints means a biochemical change, functional impairment, or pathologic lesion that negatively affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge." We did not make a change to the wording as we adopted the U.S.EPA's definition of adverse effect. We appreciate the comment regarding reserve capacity, and note that the definition of adverse effect encompasses this consideration.

2. Selection of the toxicological hazard traits (Articles 2 and 3 in the proposed regulation and Section V, Articles 2 and 3 in the Initial Statement of Reasons).

Comment: The hazard traits provided are thorough in terms of scope. Also, the definitions presented are judged to be both accurate and clear in both documents. An exception I noted is for Article 3's Section 69403.14 on Reactivity in Biological Systems in the proposed regulation, and also in the relevant section in the Initial Statement of Reasons. Given that the Clearinghouse seeks to provide information relevant to hazard traits associated with consumer products, the wording in these

sections could consider noting the importance of consumer product-related reactivity taking place in the surroundings of an individual that could impact hazard. Examples of indoor air-related publications, including research from UC Berkeley and Lawrence Berkeley Laboratory, include (apologies for noting something that I authored; however, it is directly related to this comment and is in the Information Resources in Toxicology book as a topic):

Information Resources in Toxicology (Fourth Edition)

2009, Pages 269-279. Asish Mohapatra and Pertti J. Hakkinen. Chapter 30 - Everyday Exposures. **Excerpts:** "A recent area of strong research interest is the study of indoor air chemistry, including the reactions that can occur between ozone and the chemicals used in cleaning products, air fresheners, and paint. For example, the terpenes widely used in consumer products can react with ozone under product use conditions, leading to formation of formaldehyde, hydroxyl radical, and secondary organic aerosol (very small particles that can be inhaled).

Other examples where indoor air reactivity is discussed include (please especially note the first publication on "Hazard assessment of chemical air contaminants measured in residences"):

(University of California, Berkeley and Lawrence Berkeley Laboratory) Logue JM, McKone TE, Sherman MH, Singer BC. Hazard assessment of chemical air contaminants measured in residences. Indoor Air (2011) 21:92-109. http://www.ncbi.nlm.nih.gov/pubmed/21392118 Key excerpt: "Practical implications: This analysis identifies key chemical contaminants of concern in residential indoor air using a comprehensive and consistent hazard-evaluation protocol. The identification of a succinct group of chemical hazards in indoor air will allow for successful risk ranking and mitigation prioritization for the indoor residential environment. This work also indicates some common household activities that may lead to the acute levels of pollutant exposure and identifies hazardous chemicals for priority removal from consumer products and home furnishings."

(University of California, Berkeley) Nazaroff WW and Weschler CJ. Cleaning products and air fresheners: exposure to primary and secondary air pollutants. Atmos. Environ. (2004) 38: 2841–2865.

Sarwar G, Olson DA, Corsi RL and Weschler CJ. Indoor fine particles: the role of terpene emissions from consumer products. J. Air Waste Manage. Assoc. (2004) 54: 367–377. http://www.ncbi.nlm.nih.gov/pubmed/15061618

(University of California, Berkeley and Lawrence Berkeley Laboratory) Destaillats H, Lunden MM and Singer BC et al., Indoor secondary pollutants from household product emissions in the presence of ozone: A bench-scale Chamber study. Environ. Sci. Technol. (2006) 40: 4421–4428.

http://www.ncbi.nlm.nih.gov/pubmed/16903280

(University of California, Berkeley and Lawrence Berkeley Laboratory) Singer BC, Destaillats H, Hodgson AT and Nazaroff WW, Cleaning products and air fresheners: emissions and resulting concentrations of glycol ethers and terpenoids. Indoor Air (2006) 16: 179–191.
http://www.ncbi.nlm.nih.gov/pubmed/16683937

Response: Comment noted. We agree that there are a number of examples of chemicals in consumer products that react in indoor air to form other toxic chemicals. Note that we include reactions in indoor air to form ozone in our hazard trait ambient ozone formation. This type of information would be assessed by DTSC during the product prioritization phase of their process. Information on the toxic chemicals formed from chemicals released from consumer products should be captured by this regulation and be included in the Clearinghouse. This comment and associated references may be helpful to DTSC as they develop and implement their regulation and will be shared with them. No changes to the regulation were made based on this comment.

3. Selection of the environmental hazard traits (Article 4 in the proposed regulation and Section V, Article 4 in the Initial Statement of Reasons).

Comment: Although this is not very much within my areas of experience and expertise, the selection of the environmental hazard traits and the definitions presented seem to be thorough and are accurately and clearly presented in both documents.

Response: Comment noted.

4. Selection of the exposure potential hazard traits (Article 5 in the proposed regulation and Section V, Article 5 in the Initial Statement of Reasons).

Comment: This is not very much within my areas of experience and expertise, with the exception of the “Lactational or Transplacental Transfer” and “Particle Size or Fiber Dimension” contents. The selection of the exposure potential hazard traits and the definitions presented seem to be thorough and are accurately and clearly presented in both documents.

Response: Comment noted.

5. Selection of the physical hazard traits (Article 6 in the proposed regulation and Section V, Article 6 in the Initial Statement of Reasons).

Comment: The physical hazard traits selected and described from the sources noted focus on combustion facilitation, explosivity, and flammability. The use of these traits is judged to be both quite thorough in the context of these documents, and they are

clearly described in both documents. Adding mention of a publication noting and discussing a broader set of possible physical hazards that consumers and others could encounter could be considered. A possible publication about this is:

> **Information Resources in Toxicology** (Fourth Edition)
> 2009, Pages 371-386. Gene Rider. **Chapter 42 - Physical Hazards**.
> **Excerpts: "**Toxicologists have traditionally been called upon to assess the chemical and biological hazard of products. However they are increasingly required to take a more holistic approach to product hazard evaluation and consider all potential hazards – physical as well as chemical. Increasing emphasis on physical hazards can be seen, for example, in the adoption of the Physical Agents directive by the European Union in 2004, recent changes in ASTM International's Toy Safety Standard addressing magnets, strangulation, and noise, and increasing awareness that injuries are the leading cause of death to children in all developed nations. The following text addresses the wide range of physical hazards associated with products. Emphasis is placed on consumer products rather than industrial or military products, although references from the latter are cited when they have clear relevance to consumer products. References have been chosen with an eye toward eliminating hazards from products. Emphasis was placed on understanding the etiology and susceptible population groups for each hazard. This review begins with an introduction to resources and organizations concerned with physical hazards of consumer products in general. Following this, specific classes of hazard are addressed individually. A hazard definition is provided for each of the specific hazard areas followed by a brief description of the scope of the hazard."

Response: Comment noted. OEHHA is required by statute to specify hazard traits, toxicological and environmental endpoints and other relevant data for inclusion in the Toxics Information Clearinghouse, to provide a database for DTSC to evaluate chemicals. The publication goes beyond identifying physical hazards of chemicals, to the material hazards from the use of a product like a toy – hazards like strangulation and noise. These types of physical hazards are not related to the inherent properties of chemicals, and therefore are not hazard traits as defined in the regulation. These types of physical hazards are beyond the scope of the regulation. This comment and associated references may be helpful to DTSC as they develop and implement their regulation and will be shared with them. No changes to the regulation were made based on this comment. .

6. Methodology for identifying strong evidence and suggestive evidence for toxicological and environmental hazard traits (Article 2, Sections 69402.2, 69402.4, and 69402.6, Article 3, Section 69403.16, Article 4, Section 69404.10 in the proposed regulation and Section V, Article 2, Sections

69402.2, 69402.4, and 69402.6, Article 3, Section 69403.16, and Article 4, Section 69404.10 in the Initial Statement of Reasons).

Comment: The methodologies presented and described are judged to be both accurate and clear in both documents.

Response: Comment noted.

7. Comments on the bigger picture:

a. Are there any important scientific issues relevant to hazard traits that have not been addressed in the responses provided above?

Something that seems to be missing in the mention of the development of the Toxics Information Clearinghouse in these documents is the need for early and ongoing consideration of the overall structure of this database. This is in terms of how the Clearinghouse's contents will be indexed beyond the structure shown in the tables of contents for the proposed regulation and in the Initial Statement of Response (e.g., see Article 1, Section 69401.1, in the proposed regulation). From reading other documents and Web site content, I know that the overall structure and contents of the Clearinghouse are under ongoing discussion.

I assume that a thorough indexing structure will be considered (or will continue to be considered) during the design and development of the Clearinghouse. Also, I assume that taxonomies (systems for classifying information from multiple documents or sources) are going to be established for use by the people designing the Clearinghouse, for those preparing the information for inclusion into the Clearinghouse, and for use by people trying to search and find information. Organizations such as the National Library of Medicine with experience in indexing and development of taxonomies could be asked to provide perspective and possible help.

Also, I trust that **"how to search"** and/or **"what to search" content** will be developed for the Clearinghouse to aid its users, including the types of information available via databases such as the National Library of Medicine's TOXNET® suite of databases (http://toxnet.nlm.nih.gov/) and the OECD's eChemPortal (http://www.echemportal.org/echemportal/index?pageID=0&request_locale=en).

Response: Comment noted. DTSC is responsible for development of the Toxics Information Clearinghouse. Discussion of the overall structure of the Clearinghouse is beyond the scope of the regulation. This comment and associated references may be helpful to DTSC as they develop and implement their regulation and will be shared with them. No changes to the regulation were made based on this comment.

Comment: Another comment is that an opportunity exists to note and emphasize the "read across" approach in these documents as a way to help identify and deal with hazard traits in the absence of some types of information for a substance. For example, this could have been noted and cited in the last paragraph of Page 51 of the Initial Statement of Reasons and also in Page 15's Subsection 69401.2(f) and 69401.2(g) which discuss other relevant data including structural and mechanistic similarity. A general publication describing the read across approach that could be noted is (apologies for noting something that I authored; however, it is directly related to this comment and is in the Encyclopedia of Toxicology as a topic):

Encyclopedia of Toxicology (Second Edition)

Pages 298-299. Pertti J. Hakkinen. Toxicity Testing, 'Read Across Analysis.'
Excerpts: "Testing requirements often mandate that certain sets of toxicological information have to be provided for new substances (e.g., 'base sets' or 'Screening Information Data Sets'). While the data typically come from animal studies and *in vitro* alternatives to animal testing, they can also come from use of modeling, and from human clinical or epidemiological data. A further source of information can be derived from 'read across' evaluations or analyses of the data sets available for structurally similar substances. The 'read across' approach has been accepted by some regulatory authorities, and is based on the understanding that substances with similar physicochemical property profiles will generally have similar toxicity profiles. The focus of the read across evaluation approach is on interpolation rather than extrapolation, and the rationale and data sources for the read across evaluation should be documented. For example, a read across table of data could have the related chemicals as columns, and the various types of toxicology tests and their results as the rows under each substance. Reading across the columns will highlight the amount and types of data for the group of substances. The read across evaluation will also find any gaps in the data set for a specific chemical that might be judged by the reviewer(s) to be filled by data relevant to those data gaps for the similar substances."

Other examples from the U.S. and beyond of where the **read across** approach is discussed include:

Blackburn K, Bjerke D, Daston G, Felter S, Mahony C, Naciff J, Robison S, Wu S. 2011, Case studies to test: A framework for using structural, reactivity, metabolic and physicochemical similarity to evaluate the suitability of analogs for SAR-based toxicological assessments. Regul Toxicol Pharmacol. 2011 Jun 1;60(1):120-35. http://www.ncbi.nlm.nih.gov/pubmed/21420459

Diderich R. Chemical categories: Filling data gaps by read-across and trend analysis, the OECD approach. Toxicology Letters (2009) 189 Supplement 1: S4

European Chemicals Agency (ECHA) content, e.g.,

http://echa.europa.eu/doc/press/webinars/read_across_and_categories_tatiana_netzeva_echa.pdf

Hanway RH and Evans PF. Read-across of toxicological data in the notification of new chemicals. Toxicology Letters (2000) 116 Suppl. 1: 61.

U.S. EPA's High Production Volume Web site information: http://www.epa.gov/HPV/pubs/workshop/wkshebi.htm

van Leeuwen K, Schultz TW, Henry T, Diderich B, Veith GD. Using chemical categories to fill data gaps in hazard assessment. SAR QSAR Environ Res. (2009) 20:207-20.
http://www.ncbi.nlm.nih.gov/pubmed/19544189
(Erratum in SAR QSAR Environ Res. (2009) 20:591).

Vink SR, Mikkers J, Bouwman T, Marquart H, Kroese ED. Use of read-across and tiered exposure assessment in risk assessment under REACH--a case study on a phase-in substance. Regul Toxicol Pharmacol. (2010) 58: 64-71.
http://www.ncbi.nlm.nih.gov/pubmed/20394791

Response: OEHHA appreciates the additional references. We agree that the read-across methods are important where little toxicity data exist for a chemical that is structurally similar to chemical(s) that have more robust health effects information. This comment and associated references may be helpful to DTSC as they develop and implement their regulation and will be shared with them. No changes to the regulation were made based on this comment.

b. As a whole, are the proposed hazard traits, examples of environmental and toxicological endpoints and other relevant data based on sound scientific knowledge, methods, and practices?

Comment: Yes as a whole; however, I have five additional comments for consideration:

1) Where "well-conducted scientific studies" are mentioned along with publication in the open literature (e.g., see Article 1, Section 69401.2, in the proposed regulation), it seems like the term "peer reviewed" could be added before the word "open" to indicate that the desire is to use information and publications that have undergone one or more levels of peer review.

Response: The definition of well-conducted scientific studies in the regulation is "studies published in the open literature or conducted by or submitted to a local, state, national or international government agency, using methods and analyses which are scientifically valid according to generally accepted principles." We agree that studies that have been peer-reviewed are preferred. However, there is a fair amount of "grey"

literature of well-conducted scientific studies that may be useful in prioritizing chemicals and assigning hazard traits. For example, scientifically valid studies that were conducted based on generally accepted principles but not necessarily published in the peer-reviewed literature may have been submitted to a government body in compliance of a regulatory process, or may have been done by a government agency. DTSC will be establishing the Clearinghouse under SB 509 and prioritizing chemicals and evaluating alternatives under AB 1879. This comment may be helpful to DTSC as they develop and implement their regulation and will be shared with them. No changes to the regulation were made based on this comment.

2) Mention could be made of the use of "integrated testing strategy (or strategies)" and "intelligent testing." Examples of publications discussing these topics include:

Ahlers J, Stock F, Werschkun B. Integrated testing and intelligent assessment-new challenges under REACH. Environ Sci Pollut Res Int. (2008) 15:565-72.
http://www.ncbi.nlm.nih.gov/pubmed/18818964

Berg N, De Wever B, Fuchs HW, Gaca M, Krul C, Roggen EL. Toxicology in the 21st century - Working our way towards a visionary reality. Toxicol In Vitro. (2011) 25:874-81.
http://www.ncbi.nlm.nih.gov/pubmed/21338664

Hulzebos E, Gunnarsdottir S, Rila JP, Dang Z, Rorije E. An Integrated Assessment Scheme for assessing the adequacy of (eco)toxicological data under REACH. Toxicol Lett. (2010) 198: 255-62.
http://www.ncbi.nlm.nih.gov/pubmed/20633615

An example of U.S. EPA efforts related to this topic:
http://epa.gov/oppfead1/cb/csb_page/updates/2010/workshopcenturysci.html

Response: The additional references are appreciated. This comment and associated references may be helpful to DTSC as they develop and implement their regulation and will be shared with them. No changes to the regulation were made based on this comment.

3) An existing database to consider incorporating into (or linking to) the Clearinghouse when lactational or transplacental transfer information is desired (e.g., see Article 5, Section 69405.5, in the proposed regulation) is the National Library of Medicine's Drugs and Lactation Database (LactMed, fact sheet: http://www.nlm.nih.gov/pubs/factsheets/lactmedfs.html). LactMed is a part of the NLM's Toxicology Data Network (TOXNET®) suite of databases.

LactMed is a database of drugs and other chemicals to which breastfeeding mothers may be exposed. It includes information on the levels of such substances in breast milk and infant blood, and the possible adverse effects in the nursing infant. All data are derived from the scientific literature and are fully referenced, and the data are organized into substance-specific records providing a summary of the pertinent reported information and include links to other NLM databases such as the Hazardous Substances Data Bank (HSDB®, fact sheet: http://www.nlm.nih.gov/pubs/factsheets/hsdbfs.html). Users of LactMed can search by drug or chemical name, Chemical Abstracts Service Registry Number (RN), pharmacologic category, and/or subject terms. Search results can easily be viewed, printed or downloaded.

Response: Comment noted. The identification of specific chemical databases is beyond the scope of the regulation. This comment and associated references may be helpful to DTSC as they develop and implement their regulation and will be shared with them. No changes to the regulation were made based on this comment.

4) In addition to the mention of the Hazardous Substances Data Bank above, it is worth noting that HSDB's content could fit into (or be linked to) the Clearinghouse to help provide access to the wide range of "evidence for ____ trait" information, e.g., for carcinogenicity and developmental toxicity. Like LactMed, HSDB is a data file on the NLM's TOXNET®. The focus of HSDB is on the toxicology information available for chemicals, and the content is enhanced with information on human exposure, industrial hygiene, emergency handling procedures, environmental fate, regulatory requirements, and related areas. All data are referenced and derived from a core set of books, government documents, technical reports and selected primary journal literature. HSDB is peer-reviewed by the HSDB's long-established Scientific Review Panel (SRP), a committee of experts in the major subject areas within the data bank's scope. HSDB is organized into individual chemical records, and contains over 5,000 records. HSDB is also part of OECD's eChemPortal suite of participating global databases (http://www.echemportal.org/echemportal/page.action?pageID=2).

5) I want to also note with regard to the Clearinghouse and its content that TOXNET's suite of databases will continue to be enhanced during 2011 and beyond to keep up with the state of the science in toxicology, e.g., the Comparative Toxicogenomics Database (CTD) was added in early 2011. (http://www.niehs.nih.gov/news/newsletter/2011/february/spotlight-database/ and http://toxnet.nlm.nih.gov/).

Response: We are aware of these existing databases and agree they would be appropriate sources of information. The identification of specific chemical databases is beyond the scope of the regulation. This comment and associated references may be

helpful to DTSC as they develop and implement their regulation and will be shared with them. No changes to the regulation were made based on this comment.

Response to Comments of Dr. Errol Zeiger, Ph.D., J.D., A.T.S.

1. Accuracy and clarity of the definitions presented

Comment: The definitions are presented in two different forms; in the Proposed Regulations as brief statements, and in the Initial Statement of Reasons (ISOR) as extended definitions with explanations and citations. The explanations and definitions are straightforward and clear, and the justifications provided in the ISOR are complete and appropriately cited. I recommend only a few changes or clarifications.

- In the Proposed Regulations definitions, "hazard traits" appear to be defined as toxicologic or environmental effects. However, "toxicological endpoint" is then defined in terms of hazard traits, which appears to be a bit circular. In contrast, "environmental endpoints" are defined by their effects, without reference to traits. It is recommended that "for a specific hazard trait" be deleted from the toxicological definition so that it more closely parallels the environmental definition.

  - There is also a lack of parallel between environmental and toxicological in the ISOR definitions and explanations. Under 'environmental endpoints', ISOR contains the explanation "Finding environmental endpoints … is evidence that a chemical has one of the environmental hazard traits." [Subsection 69401.2(d)] In contrast, "The toxicological endpoint is an adverse manifestation of the trait …." [§ 69401.2(h)] The two definitions should parallel each other. There is a difference between being evidence of a trait (*i.e.*, associated with) and being a manifestation of that trait (*i.e.*, causal).

Response: Based on this comment OEHHA slightly reworded the definitions of environmental endpoint to make it parallel with toxicological endpoint. The definition now reads:
"An environmental endpoint for a specific hazard trait is a measured or otherwise observed adverse environmental effect in ecological systems, or in components of ecological systems, or in non-human organisms within ecological systems that indicates the presence of the hazard trait."

However, there are real differences in the types of testing and data available for these two categories of endpoints. While laboratory studies are critical to both toxicological and environmental endpoints, the latter are also based on field studies, which may include associative data. Such information is relevant and should be included in the Clearinghouse.

Comment:

- It is curious that "radioactive agent" is included in the "chemical substance" [§ 69401.2(c)] definition. This listing, which also includes degradation by-produces, would, by its wording, extend to cover radioactivity, itself, separate from its source. However, radioactive agents are not mentioned in the expanded ISOR definitions. If radioactivity byproducts (specifically, different types of radiation) are to be specifically identified in the Regulations, they also need to be addressed, and the exact substances defined and delimited (*i.e.*, is radioactivity, apart from its source substances, included in the degradation by-products) in the ISOR.

Response: The term "degradation by-products" is used generally to refer to any breakdown product including a chemical change that occurs in air, water, or soil as a result of chemical reactions or biotransformation or radioactive decay. OEHHA believes the existing definition sufficiently addresses this concern. No changes to the regulation we made based on this comment.

Comment:

- "Well-conducted scientific studies." [§ 69401.2(i)] It should be specified that the studies be peer-reviewed, to distinguish them from studies published in other, less scientifically rigorous media, or presented only at conferences. Studies published as non-peer-reviewed articles may be used if they meet the criteria (*i.e.*, "using methods and analyses which are scientifically valid …") described in the definition.

  - The ISOR makes a good point with regard to the use of well-designed and conducted studies even if they are not GLP. A similar comment can be made regarding studies that are not strictly according to OECD or USEPA Test Guidelines. Many research organizations test chemicals for non-regulatory submissions, and their published studies may be considered by the regulatory authorities when dealing with the particular test substance. Other organizations may have valid data that predate the formal guidelines. If the study is well performed, it should not be discarded because it was not strictly according to Guidelines, for example, if one or two fewer animals or Ames tester strains were used, or the requisite number of repeat tests were not conducted.

Response: The definition of well-conducted scientific studies in the regulation is "studies published in the open literature or conducted by or submitted to a local, state, national or international government agency, using methods and analyses which are scientifically valid according to generally accepted principles." We agree that studies that have been peer-reviewed are preferred. However, there is a fair amount of "grey" literature of well-conducted scientific studies that may be useful in prioritizing chemicals and assigning hazard traits. For example, scientifically valid studies that were conducted based on generally accepted principles but not necessarily published in the peer-reviewed literature may have been submitted to a government body in compliance of a regulatory process, or may have been done by a government agency. DTSC will be establishing the Clearinghouse under SB 509 and prioritizing chemicals and evaluating alternatives under AB 1879. This comment may be helpful to DTSC as they

develop and implement their regulation and will be shared with them. No changes to the regulation were made based on this comment.

We appreciate the concern that restricting information in the Clearinghouse to studies that followed Good Laboratory Practice would disallow much of the available information on chemical toxicity from appearing in the Clearinghouse, which is meant to be as comprehensive as possible. Good Laboratory Practice is not equivalent to a good scientific study, although it is frequently interpreted as such. Under the statute, DTSC is charged with establishing data-quality criteria for the Clearinghouse and will likely address this issue as part of that process. No change to the regulation was made based on this comment.

Comment:

- As a general comment, the term 'trait(s)', as it is applied in these regulations, appears to be specific to California regulations and is not, to the best I can determine, used anywhere else to describe adverse biological or ecological properties of substances. "Trait" also implies that the indicated toxic or ecological effect is an inherent property of the substance. This is not only misleading but also potentially alarming. There are many chemicals (that have hazard traits) that are required to sustain life and/or are produced during normal metabolism. The Agency might want to consider adopting a different term.

Response: The legislation that OEHHA is implementing in this regulation coined the term "hazard trait." We have undertaken to define "hazard trait" as clearly as possible within the context of the overall intent and purpose of the statutory scheme created by SB 509 (Simitian, Chapter 560, Statutes of 2008) and AB 1879 (Feuer, Chapter 559, Statutes of 2008). OEHHA does not have the legal authority under these two statutes to simply choose a different term.

The hazard traits included in the regulation should be regarded as inherent properties of chemicals. We disagree that it is misleading or alarming to imply that the hazard trait is an inherent property. Many toxic chemicals are produced during normal intermediary metabolism; the simple fact that they are produced naturally does not rid them of toxicity.

Finally, we understand the concern about alarm when a less informed person views the assignation of a hazard trait to a chemical, especially in view of the wide variability in potency of chemicals to produce toxic effects. However, based on this and other comments OEHHA received, we added an article to the regulation that encompasses dose-response information so that such information will become an integral part of the Clearinghouse. The public understands that some substances (for example, the over-the counter pain medication ibuprofen) are both beneficial and harmful depending on dose, therefore, the addition of dose-response information may lower the level of "alarm" generated by assigning a particular hazard trait to a given chemical.

2. Selection of the toxicological hazard traits

Comment:
The selection of the toxicological hazard traits appears reasonable and inclusive of health effects of concern, and of many of the mechanisms leading to those health effects. For my evaluation, I concentrated on those traits with which I am most knowledgeable – carcinogenicity, developmental toxicology, reproductive toxicology, endocrine toxicology, genotoxicity, and reactivity in biological systems.

- Carcinogenicity. The ISOR defines carcinogenicity as malignancy [§ 69402.1(a)] based on the IARC definition, whereas the Proposed Regulations also includes benign [§ 69402.1(b)] tumors. Although as noted in the ISOR, benign tumors are considered by agencies in arriving at a carcinogenicity classification, the text does not indicate whether benign tumors, by themselves, are sufficient for the classification. The blending of US (*i.e.*, NTP, EPA) and international (IARC) rules, can be confusing because, in general, the US agencies will consider benign tumors, by themselves, as sufficient for classifying a substance as a carcinogen, whereas the IARC will also require malignancy. The role and contribution of benign tumors, and whether they can stand alone, to the classification needs to be better defined.

Response: OEHHA purposely included both U.S. and international criteria for classification to be as inclusive as possible for information in the Clearinghouse. The carcinogenicity hazard trait, like IARC and U.S. NTP, emphasizes malignancy. Toxicological endpoints for this hazard trait are benign or malignant tumors. Tumors that are benign and known to progress to malignancy provide stronger evidence for this hazard trait than other benign tumors. Note that the explanation of evidence in the NTP long term testing reports states “Clear evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.”

OEHHA’s regulation does not classify any specific chemical as having any particular hazard trait. Rather, it specifies the types of information to be included in the Clearinghouse. DTSC is charged with identifying and prioritizing chemicals for its consumer-products regulatory program. No changes to the regulation were made based on this comment.

Comment:

- The Proposed Regulations identify a number of findings that would lead to a classification of “suggestive evidence of carcinogenicity.” The first three of these [§§ 69402.2(b)(1)(2)(3)] are based on evidence of cancer in animals, and are valid, whereas the next three [§§ 69402.2(b)(4)(5)(6)] are based solely on the mechanistic considerations of genotoxicity, general mechanistic evidence, and QSAR methods. Although, I agree that positive results in these latter three procedures can constitute suggestive evidence of carcinogenicity, unlike the

animal tests, they are not tests for carcinogenicity and not proof of carcinogenicity. As the Proposed Regulations are currently worded, I am concerned that a result from one of these mechanistic studies suggesting a positive response could be given equal weight to an animal study showing a positive response. This is not justifiable given the variety of different studies and systems (especially genotoxicity and QSAR) and their varying levels of predictability for carcinogenicity.

- Although IARC's use of mechanistic information is cited as a justification for the inclusion of these studies, IARC does not use these studies for classification, but only to support an up- or down-grade in classification when there are existing, positive animal cancer studies. It is recommended that these three mechanistic categories be considered, as is done by IARC, as supporting an upgrade in classification when there is an existing, positive animal cancer study, and not at the same level of evidence as existing animal studies.

- One example of mechanistic evidence presented in the ISOR is the metabolism of a wide variety of benzidine-based dyes to benzidine, which is a known human carcinogen. This 'mechanism-based' example is accurate and valid, but in a completely different category than, for example, 'changes in physiology.' In the benzidine example, the mechanistic studies show that regardless of the dye administered, the test substance is actually benzidine. In contrast, the physiological changes, as well as genetic damage, are events leading to the development of cancer, but are far from sufficient, and far less persuasive (than the benzidine example) for induction of cancer.

– The QSAR explanation in ISOR [§ 69402.2(b)(6)] reads as if EPA's OncoLogic program is being recommended to the exclusion of many other programs that may be no less robust. Although those other programs may be proprietary, they are widely used and relied upon by industry and US Government regulatory bodies. I agree that proprietary systems should not be mentioned by name because it would imply endorsement of the named systems to the exclusion of others that may not be named. However, it should be made clear that other proprietary and non-proprietary systems are equally acceptable; the only limitation should be supportive evidence showing their predictive effectiveness for the effect in question.

Response: This regulation does not identify any chemical as having any particular hazard trait, including whether a chemical is or is not a carcinogen, and does not provide criteria for DTSC to use to classify chemicals or assign hazard traits. Similarly, the regulation does not provide for chemicals to be "classified" as having strong or suggestive evidence of carcinogenicity. Rather, the examples of strong and suggestive evidence for carcinogenicity in section 69402.2 are meant to promote the inclusion of this kind of information in the Clearinghouse, and to provide some guidance to DTSC, product manufacturers and other Clearinghouse users to better understand the information relating to a given chemical and the carcinogenicity hazard trait.

The regulation does not equate the results of a cancer bioassay to structural similarity as "proof" of carcinogenicity. As the comment points out, genotoxicity, mechanistic evidence and QSAR results are identified as suggestive evidence of carcinogenicity. Other structure activity information is also identified. Section 69402.2(b) simply lists different kinds of suggestive evidence of carcinogenicity without ranking these different kinds of evidence in order of importance or determining when one kind of evidence should be given equal weighting to another. The regulation seeks to provide a broad net to capture information relevant to the hazard traits for inclusion in the Toxics Information Clearinghouse.

OEHHA does not intend to exclude proprietary or other QSAR programs from inclusion in the Clearinghouse as they may provide valuable information, particularly when accompanied by supporting information. The wording in the regulation does not restrict consideration of structure activity to QSAR models, and makes no mention of a particular QSAR model. The ISOR referred to the one used by U.S.EPA. (Oncologic) as an example. It did make any specification regarding whether or not or exclude information generated through proprietary models. The merits of using the results of any particular QSAR model in determining whether a chemical has the carcinogenicity hazard trait is beyond the scope of this regulation. We have shared these comments with DTSC, to help inform them as they implement the provisions of AB 1879.

As a point of clarification, IARC guidelines for a "Group 2B" carcinogen ("The agent is possibly carcinogenic to humans") state: "An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data." (IARC Monographs Preamble, 2006).[8] Similarly, the NTP criteria provide for the identification of a chemical as "reasonably anticipated to be a human carcinogen when "there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans."[9]

Comment:

- Developmental toxicity. Similar to my comments regarding Carcinogenicity mechanistic studies [§ 69402.4(b)], evidence from mechanistic and QSAR studies [subsections (4)-(7)] should be assigned less weight than findings in animal tests [subsections (1)-(3)].

Response: The section in question is meant to promote the inclusion of this kind of information in the Clearinghouse and to provide some guidance to DTSC, product manufacturers and other Clearinghouse users in better understanding the information relating to a given chemical and the developmental toxicity hazard trait. Mechanistic evidence and QSAR models can provide suggestive evidence of the potential for developmental toxicity. Section 69402.4(b) is not attempting to determine how different

[8] Cited in the ISOR, reference 4, also available online at: http://monographs.iarc.fr/ENG/Preamble/index.php

[9] Cited in the ISOR, page 25, also available online at http://ntp.niehs.nih.gov/?objectid=47B37760-F1F6-975E-7C15022B9C93B5A6

kinds of evidence should be weighted. This comment may be helpful to DTSC as they develop and implement their regulation and will be shared with them. No changes to the regulation were made based on this comment.

Comment:

- Reproductive toxicity. The ISOR [§ 69402.5(a); on pg. 40, last paragraph] correctly notes that developmental toxicology is a component of reproductive toxicology. It should also be noted that endocrine toxicology is a major component of reproductive toxicology (this information should also be included in the Endocrine Toxicology section [§ 69403.2]), and the inter-relationships of endocrine toxicology with reproductive and developmental toxicology should be noted. Many of the endpoints of male and female reproductive toxicity are the same as those used for evaluating male and female endocrine disruption.

  - The effects constituting 'suggestive evidence' are appropriate, with the exception of the QSAR indication [§ 69402.6(b)(6)]. Evidence from such systems are less well developed than the QSAR systems for carcinogenicity and genotoxicity, and should not be afforded equal status to results of animal studies, or even to results from relevant mechanistic studies absent convincing evidence of their effectiveness.

Response: We agree that there is interplay between the endocrine system and successful reproduction and development; endocrine toxicants can also be developmental and reproductive toxicants.

Criteria for use of information in the Clearinghouse to assign hazard traits to chemicals is beyond the scope of this regulation and the OEHHA mandate. DTSC is responsible for prioritizing chemicals and can use information on hazard traits as well as other information. The section in question is meant to promote the inclusion of this kind of information in the Clearinghouse and to provide some guidance to DTSC, product manufacturers and other Clearinghouse users to better understand the information relating to a given chemical and its possible hazard traits. Section 69402.6(b) is not attempting to determine how different kinds of evidence should be weighted.

As discussed in the comment, mechanistic evidence can provide suggestive evidence of the potential for reproductive toxicity. Although the peer reviewer expresses concern about the accuracy of existing QSAR models for reproductive toxicity, OEHHA believes information from structure activity studies, including from scientifically valid QSAR models, should be included in the Clearinghouse. Much research and effort is currently going into QSAR modeling for many different toxicological endpoints, including reproductive toxicity, and in the future there will likely all have to be more scientifically value structure activity approaches available for use. OEHHA does not intend to give equal status to all QSAR models for endocrine toxicity and recognize that as in all predictive models, there is variability in predictivity.

This comment may be helpful to DTSC as they develop and implement their regulation and will be shared with them. No changes to the regulation were made based on this comment.

Comment:

- Endocrine toxicity. This section [§ 69403.3] of the ISOR should refer back to the overlap between endocrine toxicity and developmental and reproductive toxicities.

Response: We agree that endocrine toxicants can interfere with successful reproduction and development. The ISOR covers this issue sufficiently. No changes to the regulation we made based on this comment.

Comment:

- Although I do not provide specific comments on epigenetic toxicology [§ 69403.4], I have concerns with its incorporation among the other toxicity traits. Epigenetic changes are a required, normal component of organism development and not hazardous, per se. Although epigenetic effects are emerging as an important mechanism of toxicity, to the best of my knowledge there are, as of now, no standard tests to measure such effects and no clear consensus on what changes or level of change, and at what life stage of the organism, would constitute an adverse effect. I am concerned that, for example, a chemical such as the amino acid, methionine, which is involved with DNA methylation, would be considered hazardous because changes in dietary levels could lead to changes in DNA methylation state based on animal or in vitro tests. At the present time, I believe it is premature to list epigenetic effects as a hazard trait equivalent to the other traits in this section [§ 69403].

Response: We agree that epigenetic toxicity is a relatively new field and that test methods are still developing. Nonetheless, we do not agree that it is premature to include epigenetic toxicity as a hazard trait. To the extent that information is available, it should be included in the Clearinghouse. The definition of the epigenetic hazard trait in the regulation indicates that an epigenetic change induced by a chemical exposure leads to an adverse effect. The definition is: “The epigenetic toxicity hazard trait is defined as changes, at the cellular or organism level, in gene expression or gene function that do not involve changes in the DNA sequence and contribute to adverse effects in an organism, following exposure to a chemical substance.” The example given of changing dietary levels of the essential amino acid, methionine, would not cause methionine to be listed as having this hazard trait. A deficiency of methionine might be hazardous if severe enough, but this would not cause DTSC to label methionine as having a hazard trait based on this definition. This comment may be helpful to DTSC as they develop and implement their regulation and will be shared with them. No changes to the regulation were made based on this comment.

Comment:

- Genotoxicity. The inclusion of sister chromatid exchanges (SCE) on an equal footing with the other genetic endpoints [§69403.5(b)] is not recommended. Unlike the other endpoints identified, less is known about the causes or consequences of SCE. They are also known to often be formed in the absence of direct DNA damage or as a consequence of test protocol factors and artifacts. This has led to the decision by the OECD to 'retire' its 1987 SCE Test Guideline, and to the absence of SCE tests from those currently considered or recommended by regulatory authorities in the US and elsewhere. The current thinking about SCE is that they may serve as a biomarker of chemical exposure, or as an indicator of non-specific DNA damage. As such, SCE are more appropriately placed with the commonly used DNA damage endpoints. As a result, the 2nd sentence in the first paragraph on pg. 64 of the ISOR ("It is common to perform mammalian evaluation of SCE *in vivo* or *in vitro*.") is incorrect and should be deleted.

- Bacterial DNA damage is currently listed among the "commonly used" assays of DNA damage. This endpoint should be deleted because the tests used have been shown to lack reproducibility across laboratories and some of them are not well defined genetically, *i.e.*, the repair-proficient and repair-deficient cell lines are not isogenic. Another factor to consider is that the tests are no longer being performed routinely except, perhaps, as an initial screen prior to performing standard genetic toxicity tests.

Response: Regarding giving equal weight to SCE and other genotoxicity endpoints, the regulation does not imply any weighting with respect to the different toxicological endpoints for genotoxicity. The regulation indicates data on SCE should be included in the Clearinghouse. Data on SCE is still used to evaluate genotoxicity, although other toxicological endpoints for genotoxicity may provide stronger evidence. Authoritative organizations still use SCE as evidence for genotoxicity including the International Agency for Research on Cancer (see their Preamble, 2006, citation 67 in the ISOR). The ISOR states "Sister chromatid exchanges (SCE) may be due to errors in the chromosomal replication process during the S phase of mitosis". There is evidence that indicates that increased SCEs may in fact reflect genotoxicity in the absence of DNA damage caused by covalent binding or oxidation. Test guideline TG479 (Genetic Toxicology: In vitro Sister Chromatid Exchange Assay in Mammalian Cells) is still available on the Organisation for Economic Cooperation and Development (OECD) Web site (see attachment). Additionally, while streamlining of some testing programs (e.g. the National Toxicology Program) has eliminated the SCE assay from their standard testing regime, recent open literature research still includes data on the ability of potential genotoxicants to induce SCEs.

Bacterial DNA damage assay data (including comet assay and SOS system data) is currently being reported in peer-reviewed publications, and bacterial DNA damage assay methods development is still being actively pursued (Chen *et al*., 2011; see attachment). This indicates that bacterial DNA damage assays are valid as a toxicological endpoint for the genotoxicity hazard trait, and results from such assays should be included in the Clearinghouse.

This comment may be helpful to DTSC as they develop and implement their regulation and will be shared with them. No changes to the regulation were made based on this comment

Comment:

- Reactivity in Biological Systems. This trait is not well defined or delimited. The ability to "catalyze electron transfer" [§ 69403.14(b)] can refer to a myriad of natural, and endogenous chemicals, including some vitamins, and processes vital for sustaining life. The Proposed Regulations should be carefully written so that molecules such as vitamins A and C, and vital cellular constituents such as cysteine and glutathione, are not considered to have this trait. Alternatively, or in addition, there should be a clear statement that the presence of this trait may just as often be beneficial as hazardous and that, unlike traits such as genotoxicity and developmental toxicity, the determination of hazard from electron transfer activity is highly context-dependent.

Response: The hazard trait Reactivity in Biological Systems, is defined in the regulation as "the occurrence of rapid reactions with molecules in the body that lead to alterations in critical molecular function and ultimately adverse health outcomes". Thus, the processes vital for sustaining life would not be included as they do not result in adverse health outcomes. While there are myriad chemical reactions that go on during normal cellular processes involving reactive intermediates, electron transport and generation of reactive oxygen species, these processes are controlled in the cell in order to generate energy and keep the cells functioning. Such processes are not resulting in adverse health effects. No changes to the regulation were made based on this comment.

3. Selection of the environmental hazard traits

This is an area that I am not qualified to address.

4. Selection of the exposure potential hazard traits

The only areas in this section that I feel qualified to address are bioaccumulation and lactational or transplacental transfer.

Bioaccumulation [§69405.2]. The definition and criteria appear to be adequate.

Lactational or Transplacental Transfer [§69405.5]. The definition and criteria appear to be adequate.

Response: Comments noted. No changes were made to the regulation based on this comment.

5. Selection of the physical hazard traits

This is an area that I am not qualified to address.

6. Methodology for identifying strong evidence and suggestive evidence for toxicological and environmental hazard traits

My comments on the methodologies for identifying evidence for toxicological hazard traits have been included in my comments on the individual hazard traits. The methodologies presented for identifying strong evidence are valid and appropriate. My concerns, however, are with the presentations of methodologies for identifying suggestive evidence.

In general, the various methods listed are all valid, but are associated with widely different levels of assurance regarding the specific trait. For example, as noted in my above comments, as the Proposed Regulations are currently written, results of an animal test for the apical endpoint, and a QSAR prediction, may be given equal weight as suggestive evidence (for human hazard). While I agree that they can both provide suggestive evidence, and be supportive of strong evidence, they do not merit, and should not be given, equal weight in the absence of strong evidence.

Another issue to be considered is that not all tests that can be used to address the same hazard trait are equal or equivalent in their abilities to identify or predict the trait. As examples, there are many in vitro and in silico tests currently available that are designed to measure what are believed to be events leading to the development of a tumor, but there is limited information from the majority of these tests as to their predictivity or their relevance for the apical endpoint. For example, in the area of genotoxicity, whereas gene mutations are considered highly predictive for cancer, tests for effects such as sister chromatid exchanges in vitro or in vivo, and chromosome aberrations in vitro, are considered to yield high positive rates but be poorly predictive for other genotoxic effects or cancer. Similarly, the QSAR systems available for genotoxic prediction can have widely differing predictive abilities depending on the algorithms they are based on, and the training sets used to develop and maintain the systems.

The ISOR, and possibly the Proposed Regulations, should recognize these differences in effectiveness among test procedures designed to address the various suggestive evidence endpoints, and caution that information on the reliability and relevance of the particular procedure, or test endpoint, needs to considered when evaluating test results or data for suggestive evidence.

Response: OEHHA understands that not all toxicity tests are equal. This regulation is identifying the types of information that should be included in the Toxics Information Clearinghouse. .

The purpose of the sections on strong or suggestive evidence for specific hazard traits is to promote the inclusion of this kind of information in the Clearinghouse and to provide DTSC, product manufacturers and other Clearinghouse users with guidance to better understand the information relating to a given chemical and its possible hazard traits. For some chemicals there will be a lot of information that has already been

reviewed by an authoritative organization. For others, there may only be a suggestion from a variety of different types of studies that the chemical has a hazard trait. However, all available evidence from studies conducted in a scientifically acceptable manner should be available in the Clearinghouse. The regulation does not attempt to determine how different types of evidence should be weighted.

This regulation does not prescribe a weight-of-evidence approach to use in evaluating whether or not a chemical has a hazard trait. We recognize that the available information has to be viewed in the overall context of the total database on a chemical in deciding whether or not a chemical has a hazard trait. This comment may be helpful to DTSC as they develop and implement their regulation and will be shared with them. No changes to the regulation were made based on this comment

Response to Comments from Dr. Bette Meek

Bette Meek, Ph.D., Associate Director, Chemical Risk Assessment, McLaughlin Centre for Population Health Risk Assessment. University of Ottawa, One Stewart St., Suite 309, Ottawa, Ont. CANADA K1N 6N5, Tel: 613-562-5800 x2105/Fax:613-562-5380, bmeek@uottawa.ca

1. Introduction*:*

Comment:
With few exceptions, the proposed regulations seem thoughtful and inclusive of relevant initiatives, nationally and internationally and reflect considerable prior input (including 4 workshops and public comment). The objective to increase public availability of information on chemical hazards through a Clearinghouse on toxicity in order to provide scientific information as a basis to evaluate chemicals in consumer products is laudable, as are critically important envisaged associated activities of prioritizing chemicals and analysis of alternatives.

And while the objectives are laudable, the bounds of the extent of consideration of hazard in development of the Clearinghouse is (perhaps, understandably) limited to identification of “intrinsic” properties, only, without specification of conditions under which identified hazards are likely to be expressed. While this may not be maximally informative in subsequent establishment of priorities, the need for early designation of undesirable intrinsic hazard traits as an important component in strategies to promote safer alternatives is recognized. However, this necessarily requires collective consideration of more predictive parameters versus toxicological test results, as a basis to more meaningfully address the significant numbers of substances in commerce for which toxicological data are limited. Several of the comments offered here address strategies and tools to meet this longer term objective, as a basis to avoid continuing bias to consideration of data rich substances.

Response: Comment noted. We appreciate and agree with the stated understanding that more predictive parameters are necessary to more meaningfully address the large

number of chemicals in commerce for which toxicological data are limited. No changes were made to the regulation based on this comment.

2. Accuracy and Clarity of the definitions presented

Comment: For the most part, the included definitions are clear, being based on thoughtful and inclusive consideration of those used nationally and internationally with transparent and reasoned rationale (pages 4 – 5 of the Proposed Regs, pages 7 – 19, Initial Statement of Reasons). A few suggestions for clarification and one addition are noted below.

While it is clearly indicated that the ***hazard traits*** included in the framework address intrinsic properties of a chemical substance, excluding dose-response and exposure estimation (pages 14 and 15 of the Initial Statement of Reasons), the specific focus of the content of the Clearinghouse in the context of hazard identification versus hazard characterization is unclear. While the framework seems progressive in recognizing "mechanistic similarity" and the implied importance of understanding how chemicals induce effects as a basis to be more predictive of human health risk, it is silent currently on how hazard and mechanistic data are appropriately combined to characterize hazard in a more predictive sense.

Response: The regulation is addressing the mandate laid out in SB 509. That is, OEHHA is to specify the hazard traits, toxicological and environmental endpoints, and any other relevant data that should be included in the Clearinghouse. Use of the information to implement the mandates of AB 1879 and reduce population exposure to chemicals of concern in consumer products is outside the scope of OEHHA's SB 509 mandate and this regulation. Thus, the regulation does not provide a process or criteria to use information to prioritize chemicals and characterize hazard. DTSC is addressing this in its Safer Consumer Products Regulation. We have shared this peer review with DTSC. No change to the regulation was made based on this comment.

Comment: It is also indicated (page 8 of the Initial Statement of Reasons) that any perturbation that would lead to toxicity and disease would be considered an ***"adverse effect"*** in the context of the U.S. EPA definition proposed for adoption in the Regulations versus any measurable effect. In fact, toxicity is expected to result from sufficient perturbation of homeostasis (i.e., a cascade of failures of normal biological control mechanisms leading to disease). It seems unlikely, then, that early perturbations can be considered adverse in their own right but potentially with sustained exposure, could lead to adverse effect.

Response: We agree that sufficient perturbation would need to occur to produce toxic effects, but we noted in the ISOR (page 8) the following quote from the National Research Council report "Toxicity Testing in the 21st Century": "When perturbations are sufficiently large or when the host is unable to adapt because of underlying nutritional, genetic, disease or life-stage status biologic function is compromised, and this leads to toxicity and disease." Note that this is consistent with the definition of adverse effect in

the regulation and the discussion in the ISOR: The definition is:" "Adverse effect" for toxicological hazard traits and endpoints means a biochemical change, functional impairment, or pathologic lesion that negatively affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge. Thus, the perturbation must be sufficient to affect the performance of the whole organism or reduce its ability to respond to additional stressors, as noted in the NRC report the level of perturbations causing effects can differ across the population . No changes were made to the proposed regulation based on this comment.

Comment: Supporting documentation in the Initial Statement of Reasons (page 9), relevant to the definition of ***"authoritative organization"*** references "legal and administrative processes" applied to help ensure validity of their products. While some examples are provided concerning the nature of process that ensures scientific integrity (e.g., NAS, the federal government), there is no clear delineation of criteria for acceptability of products of authoritative organizations. These could include, for example, transparency of process, transparency and inclusiveness of identification of relevant data, nature of peer engagement including peer input, consultation and review in addition to public availability of products. Specification of these criteria would increase transparency of prioritization of classifications of different agencies considered in the context of strong and suggestive evidence for various endpoints. (Note also that the "French" government is erroneously distinguished here from European governments on page 9 of the Initial Statement of Reasons).

Response: We agree that authoritative organizations should have a transparent process with public availability of the product. The regulation and the Statement of Reasons presuppose that the authoritative organization has a transparent process and that the results of deliberations are publicly available. However, establishing criteria for the acceptability of various work products from authoritative organizations is beyond the scope of this regulation since it simply identifies information that should be included in the Clearinghouse. DTSC is charged with establishing data quality and test method standards for the Clearinghouse.

The reference to France as distinguished from the European Union in the referenced passage was intentional, although the wording in the ISOR for European governments was referring to the international European governments like the European Union.

These comments may be helpful to DTSC as they develop and implement their regulation and will be shared with them. No changes to the regulation were made based on these comments.

Comment: In relation to ***"well conducted scientific studies"*** (page 5 of the proposed regulations, page 18 of the Initial Statement of Reasons), I applaud particularly, proposal not to require that a study be conducted in accordance with Good Laboratory Practice (GLP) as a basis to evaluate hazard, in view of the desirability of acquiring data on the widest range of compounds and to more meaningfully focus on data relevant to more mode of action based predictive approaches.

In view of the need for more predictive technologies for hazard as a basis to avoid bias to data rich chemicals in the Clearinghouse, it is recommended that consideration be given to also referencing the definition of "adverse outcome pathway" developed by the U.S. EPA as follows: "The documented, plausible, and testable processes by which a chemical induces molecular perturbations and the associated biological responses which describe how the molecular perturbations cause effects at the subcellular, cellular, tissue, organ, whole animal and (when required) population levels of observation"[1]. The "adverse outcome pathway" including "molecular initiating events" (MIE) provides an extremely helpful construct in developing more predictive indicators of hazard consistent with the objectives of Green Chemistry approaches (see additional reference in comments below).

Response: We appreciate the acknowledgement that restricting information in the Clearinghouse to studies that followed Good Laboratory Practice would disallow much of the available information on chemical toxicity from appearing in the Clearinghouse, which is meant to be as comprehensive as possible. Good Laboratory Practice is a set of guidelines to ensure adequate quality control in the more traditional toxicity testing paradigms. Following does not necessarily ensure a good scientific study, although it is frequently interpreted as such.

OEHHA referenced the publication by Ankley et al. (2010) on adverse outcome pathways in the ISOR, page 107, when discussing the use of mechanistic data as suggestive evidence that a chemical has an environmental hazard trait. Since we do not use the phrase *adverse outcome pathways* in the regulations, inclusion of the definition is unlikely to provide clarification. Additionally, the conceptual framework of adverse outcome pathways refers specifically to ecotoxicology. Applying this concept to human health endpoints may require some adjustments to the framework.

Note, however, that DTSC is charged with prioritizing and identifying chemicals of concern and can use the Clearinghouse information for that purpose. We have shared these comments with DTSC, so that they may benefit from the reviewer's discussion of adverse outcome pathway and a construct for predictive indicators. No changes to the regulation were made based on these comments.

3. Selection of the Toxicological Hazard Traits

Comment: The list of toxicological hazard traits is long and relatively inclusive (n=14) framed predominantly on types of hazards identified in traditional toxicity testing studies in animals, with only one ("reactivity in biological systems") being more predictive in nature; Reliance on such a large number of traditional toxicological endpoints as a basis for identifying hazard traits (e.g., carcinogenicity, developmental and reproductive toxicity, cardiovascular toxicity, dermatotoxicity, hematotoxicity, hepatotoxicity etc.) versus simpler descriptors such as "reactivity in biological systems" seems likely to bias content of the Clearinghouse and as a result, priority setting and evaluation, to data rich substances.

In addition, while it is indicated in the Initial Statement of Reasons (page 21), that

"absence of data does not constitute absence of hazard", there is no indication of how chemicals with limited data will be addressed. Identification of the critical, simpler, more predictive undesirable parameters for hazard would seem to be one of the important objectives of Green Chemistry approaches. While it is recognized that establishment of repositories of information such as that envisaged in the Clearinghouse may be helpful in more meaningfully identifying some of these parameters, biasing content at the outset to data rich substances through the nature of delineated hazard traits will necessarily detract from this objective. Given the disparity of data available on hazard traits for different chemicals, it would be helpful to understand how it's envisaged to minimize content bias to data rich chemicals;

This seems an important aspect in addressing higher level objectives and one of the reasons that exposure parameters were weighted heavily in identification of priorities for assessment for human health priorities from amongst all 23,000 entries on the Domestic Substances List in Canada. On the basis of relatively simple information available for all substances (i.e., simple use profiles and volume and locations of use), it was possible to relatively rank all 23,000 Existing Substances in relation to their potential for exposure, ensuring their unbiased consideration.

Interestingly, also, in categorization (i.e., priority setting for assessment) of the Domestic Substances List in Canada, hazard classifications of authoritative organizations for carcinogenicity, genotoxicity and reproductive/developmental toxicity, where available, correlated well with reactivity of the compounds.

Response: We appreciate and share the concern that the Clearinghouse could be dominated by data-rich substances. In identifying the hazard traits, however, we envision a relational structure which incorporates data from both traditional toxicity testing paradigms and non-traditional or non-apical test methods and strategies. For the many chemicals with little toxicity information, it will indeed be a challenge for DTSC to consider these as fully as possible in the Clearinghouse. The issue of bias to data rich substances is a thorny problem. This situation should improve over time as information from newer toxicity testing paradigms becomes available.

A different issue arises when considering how to use the data to prioritize chemicals. As noted above, this regulation does not prescribe methods or criteria for using data to prioritize chemicals, which is the subject of a different regulatory process being conducted by DTSC. In identifying and prioritizing chemicals for its regulatory program, DTSC will have the latitude to consider parameters such as exposure and volume of use. We have shared these peer review comments with, DTSC, which is responsible for the prioritization of chemicals of concern and subsequent evaluation of consumer products. No changes were made to the proposed regulation based on this comment.

Comment: Specification of such a large number of toxicological hazard traits may also complicate codification of data from encompassing studies in the Clearinghouse. Consideration of patterns within and across systems is critical in interpretation of endpoint specific data and provides important clues about how chemicals may be inducing effects. For example, it's appropriately indicated in the Initial Statement of

Reasons (page 7) that “Thus some hazard traits are indicative of other hazard traits” with relevant examples being provided throughout the text (e.g., perturbation of the thyroid axis leading to neurodevelopmental effects. Pg. 37) but it is unclear how this interdependence will be universally addressed in a hazard characterization/mode of action context across endpoints. For example, in a more predictive mode of action context, available data on patterns of carcinogenicity and genotoxicity are jointly considered as a basis to delineate potential molecular initiating (MIEs) and key events in a hypothesized adverse outcome pathway between exposure and tumours. The initial chemical – biological interaction can then be modelled, as a basis to be more predictive for a wider range of chemicals. The likelihood of mutation being an early, rate limiting key event (i.e., acting through a mutagenic mode of action) is also addressed in this manner.

Consideration of the interrelationship of endpoints (e.g., cancer and genotoxicity) is also critically important in considering weight of evidence analysis as a basis to interpret the output of existing predictive models, such as quantitative structure activity analysis, for both statistically based models and those with mechanistic underpinning (i.e., those where MIEs have been identified). Output, for example, for both cancer and genotoxicity is considered based on weight of evidence criteria such as consistency and biological plausibility; output of individual models is also weighted based on the nature of the relevant training sets and applicability domains, specificity, sensitivity, etc.

In addition, subdivision of the hazard traits into such a large number of different types of largely traditional toxicological endpoints could be considered somewhat incongruent with transition to more progressive testing strategies, to address earlier often common manifestations of effects relevant to several organ systems.

Response: As noted above, this regulation does not proscribe methods or criteria for using data to prioritize chemicals, which is the subject of a different regulatory process being conducted by DTSC. These comments may be helpful to DTSC as they develop and implement their regulation and will be shared with them. No changes to the regulation were made based on this comment

4. Selection of the Environmental Hazard Traits

While this is not my area of expertise, I note the interdependence of several of the toxicological hazard traits identified here to those related to human health (e.g., domesticated animal toxicity, wildlife growth, survival and reproductive impairment). Generic content of the comments on selection of the Toxicological Hazard Traits above apply here, also – e.g., bias to data rich substances, patterns within and across effects and the need for simple, predictive descriptors; In relation to the latter, it’s unclear, for example, why “reactivity in biological systems” wouldn’t also be relevant here.

Response: Comment noted. We agree that reactivity in biological systems is relevant to environmental hazard traits, and is encompassed in these hazard traits. The issue of bias to data rich substances is a thorny problem. We hope this problem

will be addressed over time by keeping the Clearinghouse up to date with information from newer toxicity testing paradigms as it becomes available. No changes were made to the regulation based on this comment.

5. Selection of the Exposure Potential Hazard Traits

Inclusion of surrogates of exposure as “hazard traits” for the Green Chemistry initiative is progressive and laudable. Their definition as «properties of chemicals that increase exposure of humans and wildlife once those chemicals are released into the environment” is also clear and appropriate.

The basis for enthusiastic support of their inclusion relates to experience in categorization of the Domestic Substances List in Canada[2], that surrogates of exposure are likely to be much more discriminating in priority setting than those related to hazard, *per se.* (i.e., There is much greater variation in potential for exposure across chemicals than there is in potency for critical endpoints). In addition, availability of data on surrogates of exposure is likely to be much more even across chemicals (i.e., there is less likelihood of bias to data rich chemicals).

I wondered, though, whether other relatively simple parameters were considered for inclusion, such as molecular weight (preventing absorption), lipophilicity as measured by log octanol water partition coefficients (related to absorption, lactational transfer and bioavailability), and some measure of potential for release, given likely application in products (i.e., to what extent the substance is likely to be bound). For the latter aspect, it’s recognized that “classification of a chemical substance as having a hazard trait does not depend on its potential uses” (Page 117, Initial Statement of Reasons); It’s unclear, however, how use pattern analysis and likelihood of release in products will be addressed in priority setting and analysis. (Could this be addressed, for example, in the envisaged product ingredient network?).

Response: OEHHA appreciates the insights from the reviewer on the Canadian prioritization process and the statements regarding utility of surrogate measures of exposure.

As regards relatively simple parameters such as Kow and molecular weight, based on this and other comments, OEHHA has added Article 7 “Additional Relevant Data to be included in the Clearinghouse”, and included physicochemical properties as relevant data. These are not hazard traits in and of themselves, but are useful information that will inform DTSC’s regulatory process, including chemical prioritization and alternatives assessment.

Defining the ways in which the information in the Clearinghouse will be used in prioritization and subsequent regulatory activities is beyond the scope of the regulation. This comment may be helpful to DTSC as they develop and implement their regulation and will be shared with them. No changes to the regulation were made based on this

comment

6. Selection of the Physical Hazard Traits

Again, this lies outside of my area of expertise, but seemingly reflects important considerations relevant to potential hazards in consumer products. Harmonization with the GHS is helpful.

Response: Comment noted. No changes to the regulation were made based on this comment.

7. Methodology for Identifying Strong Evidence and Suggestive Evidence for Toxicological and Environmental Hazard Traits

Consideration of the strength of evidence for various hazard traits through distinction between strong and suggestive evidence is helpful. Inclusion of only two categories minimizes complexity, while indicating the need to consider and appropriately weight different types of information. Compatibility with global classification schemes has also seemingly been maximized, with justifiable rationale, where this is not the case.

Structuring on the basis of the framework used by the International Agency for Research on Cancer with endpoints that are manifestations of the trait and other relevant data that provide less direct evidence aligning in large measure with the strong and suggestive categories also seems appropriate. Reliance on assessments of other agencies, organized hierarchically followed by data, for which sources for the latter are also hierarchically considered moving from *in vivo* evidence in animal studies addressing hazard identification to mechanistic data to predictive models, also seems sensible.

Subdivision of the toxicological hazard traits into separate articles addressing carcinogenicity, developmental toxicity and reproductive toxicity versus other toxicological hazard traits, also seems appropriate, given the extent of consideration of classifications of the former by international and national agencies.

However, text in the Proposed Regulations and Initial Statement of Reasons is restricted to the nature of specific types of available data that may be considered in the category of “strong” or “suggestive” evidence. It does not address the critical interplay of all sources of data in robustly considering weight of evidence or the need for integration of mechanistic data at early stage as a basis to be more predictive of risk. Important in this context are traditional criteria or factors for consideration of weight of evidence in hazard characterization which have been applied widely both nationally and internationally[3]. These include consistency[4], specificity and biological plausibility.

Guidance in considering the appropriate extent of evidence in the “suggestive” category is also limited; There is, for example, repeated reference to consideration of mechanistic data indicating hazard potential from cell-based, tissue-based or whole

organism-based assays showing perturbation of known physiological, biochemical or other pathways. And while this is forward looking from the perspective of incorporating evolving methodologies to characterize adverse outcome pathways (i.e., key events in mode of action), criteria or factors to take into consideration in considering what constitutes meaningful perturbation are not specified. For example, there is reference (page 47 of the Initial Statement of Reasons) to endocrine toxicity via mechanisms likely to be involved in reproductive toxicity providing evidence of reproductive toxicity, though it is additionally considered that: "Single measurements of hormonal changes may be insensitive indicators of any damage because of large normal variability in females"; There is also repeated reference in the Initial Statement of Reasons to results of gene expression arrays, principally in the context of understanding genes in various systems targeted by specific chemicals

In relation to "suggestive" evidence, there is also repeated reference to predictive (in particular, quantitative structure activity analysis) methods for, for example, carcinogenicity, developmental toxicity and reproductive toxicity. Reference is to "validated" Quantitative Structure Activity Analysis models with no indication of the basis for "validation" (This requires explicit delineation). In general, such models are not "validated" *per se;* rather, their appropriate application is considered in the context of specified purpose (priority setting, screening, etc.) and consideration of principles such as those specified by OECD including a defined endpoint, an unambiguous algorithm, a defined domain of applicability, appropriate measures of goodness-of–fit, robustness and predictivity and a mechanistic interpretation[5], if possible.

Factors to be considered in assessing collective weight of evidence of output of predictive models are also not addressed. These include mechanistic underpinning (i.e., identification of a molecular initiating event), the nature of the relevant training sets and applicability domains, specificity, sensitivity, etc. Interestingly, in this context, for example, there is no reference to QSAR, specifically, in relation to genotoxicity, where its application is most justified, in light of mechanistic underpinning and relatively large training sets, due to availability of results of *in vitro* assays.

It might also be helpful to characterize the difference in weight of evidence for strong vs. suggestive evidence in the context of degree of confidence/uncertainty. Similarly, I wondered if there had been any thought given to specification of relevant degrees of uncertainty for various datasets supporting hazard for inclusion in the Clearinghouse.

There is also repeated reference to structural and mechanistic similarity to known toxicants in relation to suggestive evidence for "Other Toxicological Hazard Traits" but no indication of international sources of information on category approaches[6] or how it might be used.

Response: These comments are well-taken and thoughtful. However, the inclusion of methods and criteria for weighing the significance of data is beyond the scope of this regulation. For example, data-quality standards are the responsibility of DTSC, as mandated by SB 509.

We recognize that when evaluating whether or not a chemical possesses a specific hazard trait, all available data must be considered and weighed. However, that is not the subject of this specific regulation, which is limited to specifying the hazard traits, endpoints and other relevant data that should be included in the Clearinghouse. OEHHA's intent in identifying strong and suggestive evidence in this regulation is to promote the inclusion of this type of information in the Clearinghouse and to provide general guidance to DTSC, product manufacturers and other Clearinghouse users in better understanding the information relating to a given chemical and its possible hazard traits. . We have shared these reviewer comments and references with DTSC, which is responsible for determining specific approaches to be used in determining whether a chemical exhibits a hazard trait.

We removed the word "validated" in front of "quantitative structure activity models" because the reviewer is correct that the models are validated within the domain of chemicals that underlie the model and consideration of appropriate application in specific contexts must be part of evaluating any given substance.

8. The Big Picture*:*

In reading the regulation, are there any important scientific issues relevant to identifying hazard traits that have not been addressed in response to the points listed above?

Comment: While there is recognition that methods to predict hazard are evolving, suggested content of the Clearinghouse for hazard traits is (likely necessarily) delineated primarily on the basis of methods and endpoints considered in traditional toxicity testing studies in animals. There is less development of considerations related to predictive properties as a basis for characterizing undesirable characteristics of chemicals, as a basis for minimizing bias to consideration of those which are data rich (see also comments in response to other questions above).

Response: Comment noted. The issue of bias to data rich substances is a thorny problem. We hope this problem will be addressed over time by keeping the Clearinghouse up to date with information from newer toxicity testing paradigms as it becomes available. No changes to the regulation were made based on this comment.

Taken as a whole, are the proposed hazard traits, examples of environmental and toxicological endpoints and other relevant data based on sound scientific knowledge, methods and practices?

It seems likely that content here could be additionally developed to address principles for transparent and consistent consideration of weight of evidence for hazard and to

incorporate recent developments internationally in the development and application of tools such as quantitative structure activity analysis (see also comments in response to other questions above).

OEHHA Response: We recognize that when evaluating chemicals for determining whether they possess a hazard trait, one must weigh the totality of the data on a chemical. However, the criteria for weighing evidence to assign a hazard trait is beyond the scope of this regulation. We have shared these reviewer comments with DTSC, so that they may benefit from these comments in their work implementing AB 1879. No changes were made to the regulation based on this comment.

Footnotes of reviewer (Dr. Meek):

[1] Ankley, G.T., et al. (2010). "Adverse Outcome Pathways: A Conceptual Framework to Support Ecotoxicology Research and Risk Assessment." Environmental Toxicology and Chemistry 29(3): 730-741.

[2] http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/final_framework-int-cadre-eng.php

[3] See for example, Boobis et al. (2008) Crit. Rev. Toxicol. 38 87-96 and http://epa.gov/cancerguidelines/.

[4] While not addressed explicitly, the need for some consistency in relation to “Other Toxicological Hazard Traits” is implicit in the specified need to have two or more well conducting scientific studies demonstrating the hazard trait.

[5] See, for example, http://www.oecd.org/dataoecd/33/37/37849783.pdf; http://www.oecd.org/dataoecd/45/52/40705314.pdf

[6] See, for example, http://www.oecd.org/document/23/0,3343,en_2649_3436

ALTERNATIVES DETERMINATION

In accordance with Government Code, section 11346.9(a)(7), OEHHA has considered available alternatives to determine whether any alternative would be more effective in carrying out the purpose for which the regulations were proposed. OEHHA has also considered whether an alternative existed that would be as effective as and less burdensome to affected private persons than the proposed action. OEHHA has determined that no alternative considered would be more effective, or as effective and less burdensome to affected persons, than the proposed regulatory amendments.

LOCAL MANDATE DETERMINATION

OEHHA has determined this regulatory action will not impose a mandate on local agencies or school districts nor does it require reimbursement by the State pursuant to

Part 7 (commencing with Section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. This regulation simply specifies hazard traits and environmental and toxicological endpoints and other relevant data that are to be included in the Toxics Information Clearinghouse to be developed by the Department of Toxic Substances Control, pursuant to Health and Safety Code section 25256, et seq.